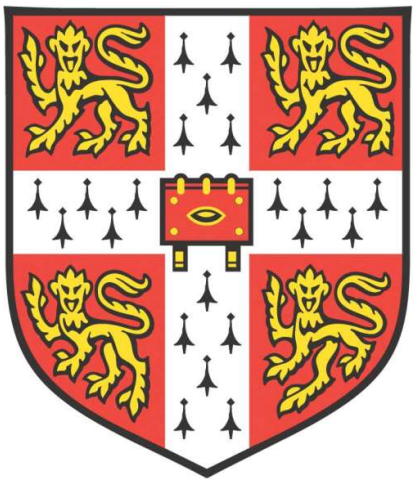
INCIDENCE OF STEAL PHENOMENA AND STEAL SYNDROME IN PATIENTS WITH ARTERIOVENOUS FISTULAE



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DECLARATION

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. It does not exceed the prescribed word limit for the relevant Degree Committee.

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INCIDENCE OF STEAL PHENOMENA AND STEAL SYNDROME IN PATIENTS WITH ARTERIOVENOUS FISTULAE

MINGZHENG AARON GOH

SUMMARY

This thesis aims to examine three key questions:

1. Can digital finger pressure measurements and the derivative digital brachial pressure index help to identify patients at risk of arteriovenous access ischaemic steal?
2. Is it possible to reduce reported rates of steal and steal phenomena in autogenous fistulae located at the antecubital fossa by modifying the arterial inflow used?
3. Should elderly patients initiating haemodialysis be consigned to a more proximal antecubital fossa (brachial) fistula, or is a more distal wrist (radiocephalic) fistula an acceptable alternative?

To address these questions, the vasculature of approximately 500 patients was analysed. The work presented in this thesis examines the use of digital finger pressures as a non-invasive diagnostic modality and underscores the importance of the digital brachial pressure index in the determination of steal phenomena and arteriovenous access ischaemic steal (AVAIS). We identified the incidence of steal phenomena in our cohort, which was of a greater scale than anticipated from the existing published literature. In Chapter 3, I present the findings for a randomised controlled trial comparing the incidence of steal syndrome and steal phenomena for 2 different autogenous fistulae sited at the antecubital fossa. Our results demonstrate that patients undergoing haemodialysis via antecubital fossa fistula experience a greater incidence of steal phenomena as compared to distal fistulae, and that by utilising the proximal radial or ulnar artery as arterial inflow, lower rates of steal phenomena are evident. Finally, Chapter 4 highlights the importance of establishing timely autologous vascular access in an elderly incident population. It emphasises that this group should not be disadvantaged by the creation of a more proximal access which might hasten exhaustion of venous capital.

For Charlotte

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List of Abbreviations and Acronyms

ABPI	Ankle brachial pressure index
AV	Arteriovenous
AVAIS	Arteriovenous access ischaemic steal
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
AUC	Area under curve
BBF / BBAVF	Brachiobasilic arteriovenous fistula
BCF / BCAVF	Brachiocephalic arteriovenous fistula
CI	Confidence interval
CO	Cardiac output
CRF	Chronic renal failure
CVC	Central venous catheter
CVSO	Central venous stenosis and occlusion
DASS	Dialysis access steal syndrome
DBPI	Digital brachial pressure index
DP	Digital [finger] pressure
DRIL	Distal revascularisation interval ligation
DUS	Duplex ultrasound
ESRD	End-stage renal disease
ESRF	End-stage renal failure
FTM	Failure to mature
HAIDI	Haemodialysis access- induced distal ischaemia

NKF-DOKI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
PRCAVF	Proximal radiocephalic arteriovenous fistula
PUCAVF	Proximal ulnarcephalic arteriovenous fistula
Qa	Vascular access flow
RCF / RCAVF	Radiocephalic arteriovenous fistula
ROC	Receiver operator characteristic
RUDI	Revision using distal inflow
UBF / UBAVF	Ulnarbasilic fistula
USS	Ultrasound

PRESENTATIONS

Oral presentations

2019 Interim results of a randomised controlled trial comparing the incidence of steal syndrome in two types of antecubital fossa arteriovenous fistulae

Goh A, Liu W, Iaculli E, Ayorinde J, Pettigrew GJ. Charing Cross Symposium 2019. London.

2017 Arteriovenous Fistula Formation With Brachial Plexus Blockade: Our Unit's Experience

Goh MA, Roopra A, Hobbiger E, Jigajinni S, Shinde P, Sharma S, Dindyal S. East of England Vascular Society 2017 Summer meeting

2015 Tattoo of vascular cannulation site as a self-cannulation aid

Lagaac, R., Quian N., Meruz, R., Pritchard, N. and Goh, A. European Dialysis and Transplant Nurses Association/European Renal Care Association Conference 2015. Dresden, Germany.

2014 The challenge of haemodialysis access in patients with central venous stenosis

Goh MA, Ali JM, Lagaac R, Barlow AD, Pettigrew GJ. Shortlisted for Harvey Prize in Vascular Medicine. Royal Society of Medicine.

2013 Outcomes of primary AV fistulae in elderly patients with end stage renal failure

Goh MA, Iype S, Ali J, Pettigrew GJ. Finalist in Vascular Access Society of Britain and Ireland oral presentation prize. Liverpool.

Poster presentations

2017 Renal Access - Arteriovenous Fistula Formation and Brachial Plexus Blockade: Service Improvement in a UK NHS Foundation Trust.

A Roopra, P Shinde, S Jigajinni, S Sharma, A Goh, S Dindyal. New York School of Regional Anaesthesia International Symposium. Dubai.

2014 The challenge of haemodialysis access in patients with central venous stenosis Goh MA, Ali JM, Lagaac R, Barlow AD, Pettigrew GJ. Vascular Access Society of Britain and Ireland 2014 Annual Meeting. Stratford upon Avon. (Poster presentation)

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1 INTRODUCTION

1.1 An overview of the history of vascular access for haemodialysis

The inception of vascular surgery, vascular access and dialysis therapy are intertwined. In 1896, Jaboulay and Briau performed an arterial end-to-end anastomosis in dogs in Lyon and subsequently published their technique [1]. A decade later, Alexis Carrel, a French surgeon, introduced the three-point end-to-end and side-to-side anastomoses and was awarded the 1912 Nobel Prize in Physiology and Medicine in recognition of his work on vascular suturing techniques and the transplantation of blood vessels and organs [2].

Dr Willem J. Kolff is credited with developing the first practical artificial kidney in 1943-1945, using parts from a destroyed German airplane and American sausage casing as his semi-permeable membrane [3]. The first horizontal rotating drum artificial kidney consisted of a drum built of wooden slats, whereby cellulose tubing holding circulating blood was rotated in a 100L porcelain tank containing a “bath” of dialysate, utilising a motor from a sewing machine (Figure 1.1; Reproduced from Friedman EA, Olsen DB. Memoriam and tribute to Willem J. Kolff, founder of Artificial Organs. ASAIO J n.d.;55:181–91. [3]). This development heralded the beginning of renal replacement therapy.

Figure 1.1: Replica of Kolff’s 1943 rotating drum artificial kidney

Dr Belding H. Scribner introduced the arteriovenous (AV) shunt in 1960, which was an external shunt consisting of Teflon tubing bridging an artery and vein (Figure 1.2; Reproduced from Bode A et al: Vascular Access for Haemodialysis Therapy, Springer, Berlin, Heidelberg; 2013, p. 235–303. [4]). This allowed for dialysis to take place without further recannulation or further injections of heparin between dialysis sessions. His first patient survived for 11 years after the insertion of his first AV shunt on March 1960. This development of a permanent vascular access was a breakthrough, enabling life-prolonging maintenance dialysis to be feasible. The Scribner shunt was not without problems – thrombosis, localised and systemic infections and shunt dislodgment (with consequential torrential arterial bleeding) occurred not infrequently [5,6]. While the Scribner shunt was ultimately superseded by other forms of vascular access, its development heralded the provision of maintenance haemodialysis to the chronic end-stage renal failure (ESRF) population.

James Cimino and Michael Brescia introduced the autogenous arteriovenous fistula (AVF) in 1966 [7] as a means to avoid externalisation of the access site; this was a side-to-side radiocephalic fistula (Figure 1.3; Reproduced from Brescia MJ et al: Chronic Hemodialysis Using Venipuncture and a Surgically Created Arteriovenous Fistula. N Engl J Med 1966;275:1089–92. [7]). In total, sixteen patients underwent AVF formation, with fourteen achieving primary patency; this is still considered an admirable result by modern standards.

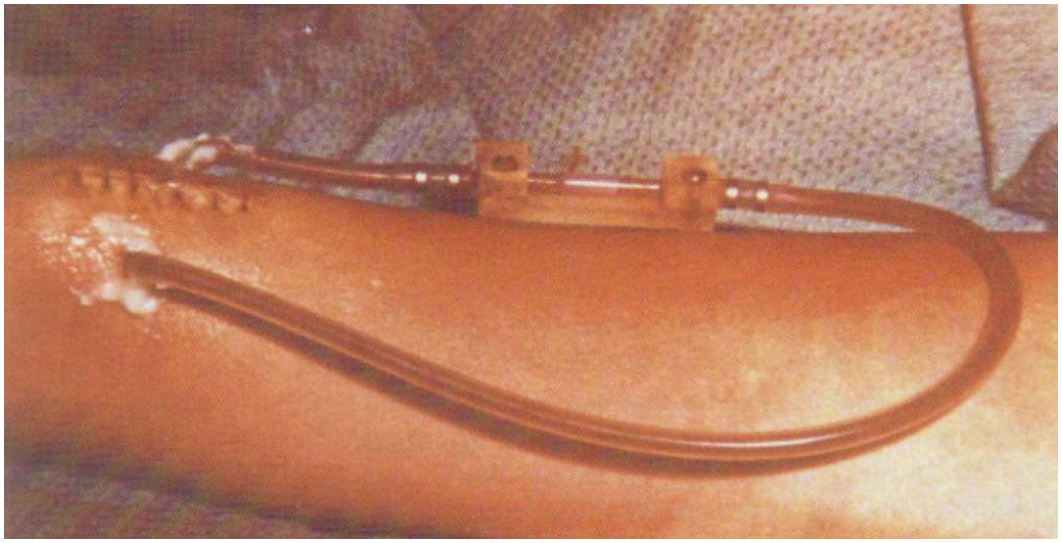


Figure 1.2: Scribner shunt

Note the two ends inserted on the left-hand side and the flexible tubing on the left functioning as the external shunt, which can then be connected to the extracorporeal circuit

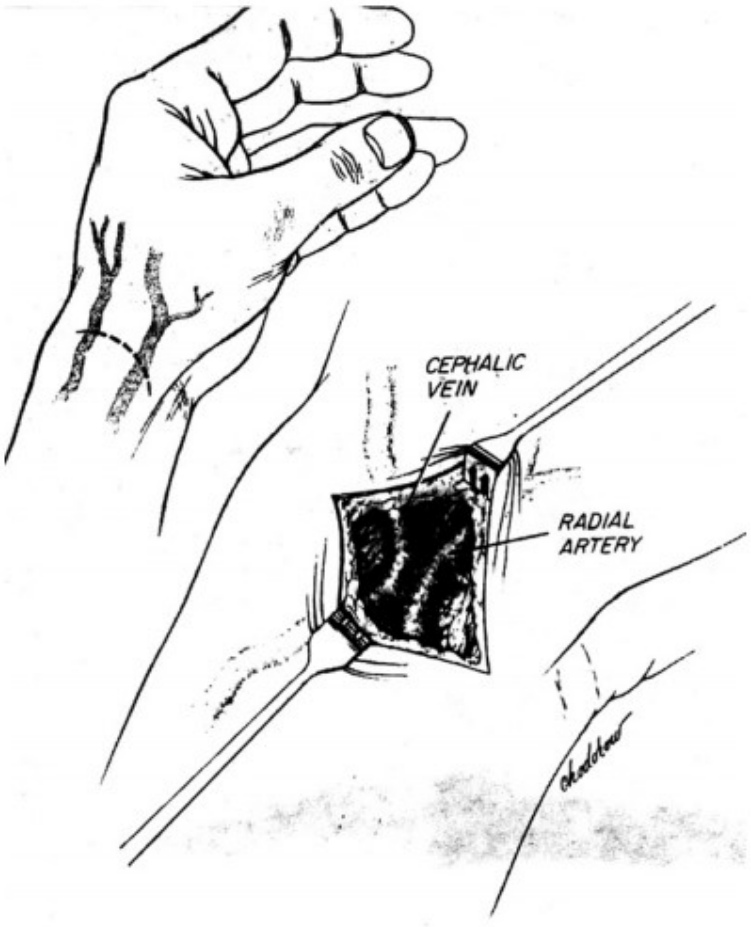


Figure 1.3: Side-to-side radiocephalic fistula

Following this ground-breaking publication, there have been multiple variations of arteriovenous fistulae. James May (Australia) proposed using a length of saphenous vein as an autogenous graft in the elbow, connecting the brachial artery to a suitable vein [8]. A variation of this method was to use the saphenous vein as an autogenous loop graft in the thigh.

The synthetic Goretex graft (W.L. Gore & associates, Elkton, MD) was introduced in the 1970s. Compared to native fistulae, these grafts matured earlier, allowing for quicker needle cannulation and thereby gained widespread popularity in the United States. However, the Goretex graft is more prone to stenosis, thrombosis and infection. A short summary of vascular access milestones is detailed in Figure 1.4.

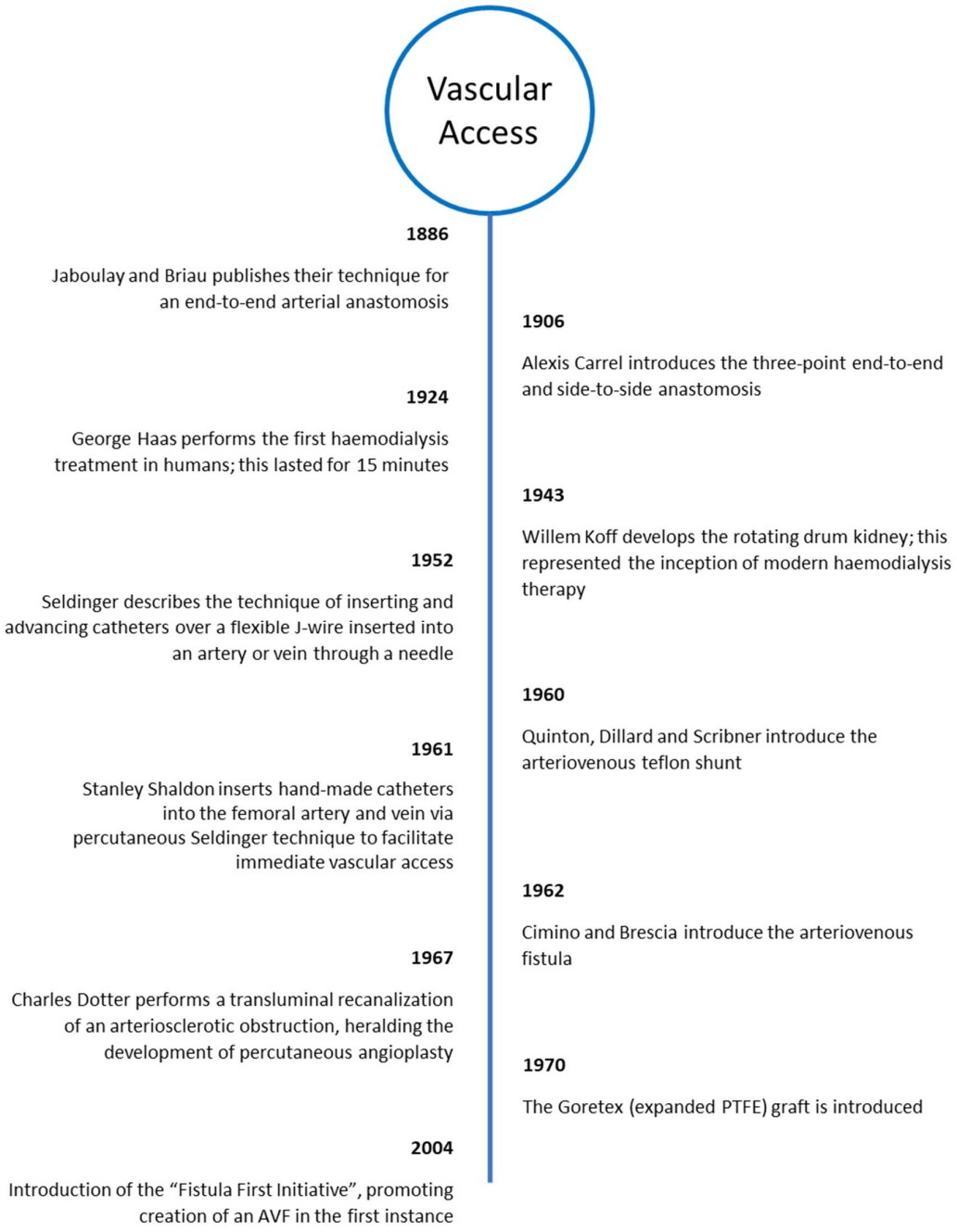


Figure 1.4: Milestones in Vascular Access

1.2 End Stage Renal Failure

1.2.1 Definition

Chronic kidney disease (CKD) is defined as an abnormality of kidney structure or loss of function which is present for more than 3 months, resulting in an estimated glomerular filtration rate (eGFR) of <90mL/min/1.73m^2, and having an impact on health [9]. It is classified into various stages based on eGFR. The terms "end stage renal disease" and "CKD stage V" are used interchangeably to describe patients with eGFR of <15mL/min/1.73m^2, indicating progression towards requiring renal replacement therapy [9].

1.2.2 End Stage Renal Failure in the United Kingdom

It is estimated that in the United Kingdom over 3 million people suffer from chronic kidney disease; of these, more than 58000 Britons receive treatment for end stage renal failure (ESRF) [10]. The incidence rate of adult patients initiating renal replacement therapy has grown steadily from 103 to 115 per-million-population in the period spanning 2004 – 2014, representing an increase of 11 percent over ten years [10,11]. This rate is comparable to many other European countries, but lower than in the USA. For patients with ESRF, renal replacement therapy offers the only means of life-prolongation [12]. Although renal transplantation is the gold standard renal replacement therapy, organ donor scarcity limits availability; in the UK the median transplant list waiting time is 3 years [13]. For patients with ESRF, dialysis is therefore usually the first line, and in many cases, destination renal replacement therapy. Options include either peritoneal or haemo-dialysis.

Kidney disease can occur at any age; however, it becomes more common in older age groups. Renal glomerular filtration rate is measured, and once it has declined below a trigger value, renal replacement is initiated. The average age of initiating renal replacement therapy has remained largely unchanged at 64 years. In contrast, the median age of a person receiving renal replacement therapy has increased from 55 to 59 years in the period spanning 2000-2015 [14]. Earlier identification and intervention following progression to renal failure, improved dialysis regimens extending survival times on

dialysis, as well as lengthening waiting lists for renal transplantation are all contributing factors to patients remaining on dialysis for a longer duration [12,15]. With increasing time spent on haemodialysis, maintenance of a functional vascular access remains challenging, especially in the context of an aging population with multiple comorbidities. For this cohort, repeated interventions and hospital admissions to restore failing vascular access are common, resulting in a poor quality of life and substantial healthcare costs [16]. Therefore, there is an urgent need to investigate strategies of prolonging venous access for the maintenance of haemodialysis; indeed vascular access is often referred to as the "Achilles heel" of haemodialysis [6,17].

End stage renal disease has a significant impact on life expectancy as well as quality of life. Risk of death at one year for individuals receiving RRT is significantly higher than that of the general population and varies according to age group; for patients aged 35-39 years the risk of death is 22 times higher than the general population and for patients aged greater than 85 years this risk is double that of the general population [14]. The need for renal replacement therapy also has significant consequences for the individual and their families. Major lifestyle modifications are necessary to accommodate treatment, which might impact the individual's ability to earn a living or to attend school or college and places a greater burden on family and caregivers. Symptoms such as malaise, fatigue and decreased appetite are common [18]. ESRF also places considerable burdens on healthcare resources and providers. Approximately 3% of the annual NHS budget is utilised to treat 61000 patients with end stage renal failure [10]. Since 2010, there has been an 18% increase in the number of UK patients commencing renal replacement therapy [14]. In 2015, a further 7800 new patients started renal replacement therapy in the UK. Outpatient haemodialysis costs between £30000 – £35000 per patient annually. Similarly, in the United States, a disproportionate percentage (7%) of the total Medicare budget is spent on patients with ESRD, which account for less than 1% of the population [19].

1.3 Current vascular access options

There are several modalities of providing adequate venous access for haemodialysis – via native (autogenous) arteriovenous fistula, synthetic graft, or long-term indwelling central venous catheter. Present key guidelines for vascular access include those published by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-DOKI) [20], UK Renal Association [21] and, most recently, the European Society for Vascular Surgery [22]. These guidelines recommend that arteriovenous fistulae (AVF) should be the preferred form of vascular access for long-term haemodialysis in patients with end-stage renal failure as they have the lowest risk of complications, lowest rate of interventions and best long term patency [17]. Furthermore, mortality is higher amongst patients who dialyse via a non-cuffed or cuffed catheter as compared to patients who dialyse via either a graft or fistula [23]. Recent data suggests that a single episode of catheter-related bacteraemia is associated with an increased mortality in the immediate post–infection period and for the following three years [17].

For individuals on long-term haemodialysis, there is a substantial risk of exhausting vascular access options following multiple access attempts. Managing a failing vascular access site remains a difficult problem. Surgical and percutaneous management of AV fistulae and grafts, as well as stents and stent grafts have been suggested as possible methods to treat access complications. Treatment of central venous stenosis and occlusions from repeated CVC insertion or prolonged usage remain challenging issues.

1.3.1 Arteriovenous fistulae

Autogenous arteriovenous fistulae (AVF) are the preferred modality for haemodialysis provision as there is a lower incidence of associated morbidity and mortality as compared to other access modalities. An AVF is created by surgically connecting a low flow, low resistance venous outflow to a high flow, high resistance arterial inflow. This fistula is then allowed to develop over 4-8 weeks [24] to allow for arterialisation of the venous component to take place which renders it sufficiently durable to be needled repeatedly. This process is termed “maturation”. During this interval, haemodynamic changes such as increased cardiac contractility, increased stroke volume, increased cardiac output,

reduced systemic vascular resistance and left ventricular dilatation or hypertrophy take place [25,26].

Current UK Renal Association guidelines recommend that AVF placement should be initiated at least 6 months prior to planned commencement of haemodialysis [21]. This is to ensure an adequate timeframe to allow for fistula maturation; this may involve salvage procedures to aid maturation or, should there be primary failure of the initial fistula, alternative fistula placement. Distal (radiocephalic) fistulae are often created in the first instance to preserve precious venous capital for subsequent proximal fistulae. In reality, there is wide institutional variation from time of referral to actual fistula creation, with early fistula formation resulting in a greater number of functioning autogenous AVFs, while delayed creation increases the risks of fistula non-maturation and consequent CVC utilisation [27–29].

There are various types of arteriovenous fistulae (AVF) and numerous ways of describing them (Table 1.1). In 2002, the Society of Vascular Surgery published recommended standards for reporting access outcomes [30], and the vascular access community has largely adopted these conventions in further reporting. Arterial inflow is reported first, followed by the venous outflow. Other descriptors such as “transposed”, “translocated”, “straight” or “looped” may sometimes be used as well. These conventions are used throughout this thesis.

There is considerable worldwide variation in the proportion of patients initiating haemodialysis via arteriovenous fistula, with the highest incidence and prevalence rates of 80% in Europe and Japan, and the lowest levels in the USA [31]. To mitigate this, in 2004, the “Fistula First Initiative” was introduced in the USA, which advocated the placement of AVFs in all suitable haemodialysis patients. This breakthrough initiative sought to improve healthcare outcomes for haemodialysis patients whilst reducing costs for the Medicare programme.

The "Fistula First" initiative is based on a multidisciplinary team consisting of nephrologists, renal access nurses and surgeons. Its goals are:

- Early identification and referral to nephrologists
- Subsequent referral to surgeons for "AVF only"
- Fashioning AVF in appropriate patients with existing AVG or CVC
- Cannulation training
- Patient and staff education
- Monitoring and surveillance, with recognition of failing access
- Continuous quality improvement review

Since the commencement of this initiative, there has been a rapid rise in the AVF prevalence rate in the USA from 24% in 1999 to just over 60% in 2012 [32].

Similarly, in the United Kingdom, current Renal Association guidelines advocate that a native arteriovenous fistula should be the vascular access modality of choice, given comparative reduced hospitalisation frequency and overall costs [21]. Within the UK, there remains wide geographical variation in local processes and service delivery, such as time to referral for access assessment, local access preference and the presence of dedicated operating lists for vascular access creation [10]. This has had a direct impact in the prevalence of vascular access modalities. What is still yet to be addressed is that fistula placement often follows CVC line insertion, which is still the access modality favoured for "crash landers" – patients who require immediate renal replacement upon presentation.

Type of access
Upper Extremity
Snuffbox [33]
Radiocephalic
Radiobasilic (transposed)
Ulnabasilic
Brachiocephalic
Brachiobasilic (single / two – stage)
Lower Extremity
Saphenopopliteal
Saphenofemoral loop
End-to side superficial femoral vein to artery upper thigh superficial femoral vein transposition loop [34]
Dorsalis pedis – long saphenous [35]
Posterior tibial – long saphenous

Table 1.1 : Types of autogenous arteriovenous fistulae

1.3.1.1 Determining AVF maturity

At present, there is no uniform definition as to what constitutes a "mature fistula". No studies have specified and validated criteria to determine when a fistula is ready for cannulation [36]. Routine preoperative vessel mapping does not appear to improve fistula maturation rates [37–39]. Some studies have suggested a minimum fistula diameter of 6mm and suitable fistula wall thickness, without defining the latter quantitatively [40]. Guidelines from the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI) have suggested that a fistula is more likely to be usable if they meet the "rule of 6s" criteria: flow greater than 600mls/min, diameter of at least 6mm, no more than 6 mm deep and discernible margins [20]. However, this is based on expert opinion rather than validated studies. Fistula maturation requires a compliant and responsive vasculature capable of dilating in response to the increased velocity of blood flowing into the newly created low resistance circuit. Successful maturation to a high volume flow circuit capable of sustaining haemodialysis typically occurs within the first few weeks after creation [41].

Following AVF creation, it is vital that the fistula be assessed by an experienced member of staff between 4-6 weeks after formation. At this point, a decision can be made as to whether the fistula is fit for cannulation, whether it should be further assessed in a further 2-4 weeks to allow for further maturation, or if further intervention (either endovascular or surgical) is required. Earlier identification and treatment of a failing fistula is required to reduce the time from fistula creation to utilisation and thereby may help to curtail the high rate of central venous catheter use for haemodialysis [24].

1.3.1.2 Fistula failure

Fistula failure can be thought of as an inability of an AVF to provide the requisite blood flow to sustain haemodialysis. It can be divided into two broad categories, early and late. Early failure comprises of fistulae which following creation were unsuitable for dialysis use, whilst late failure encompasses fistulae which were being used for dialysis but subsequently failed. Failure subcategories are outlined in Figure 1.5 [42].

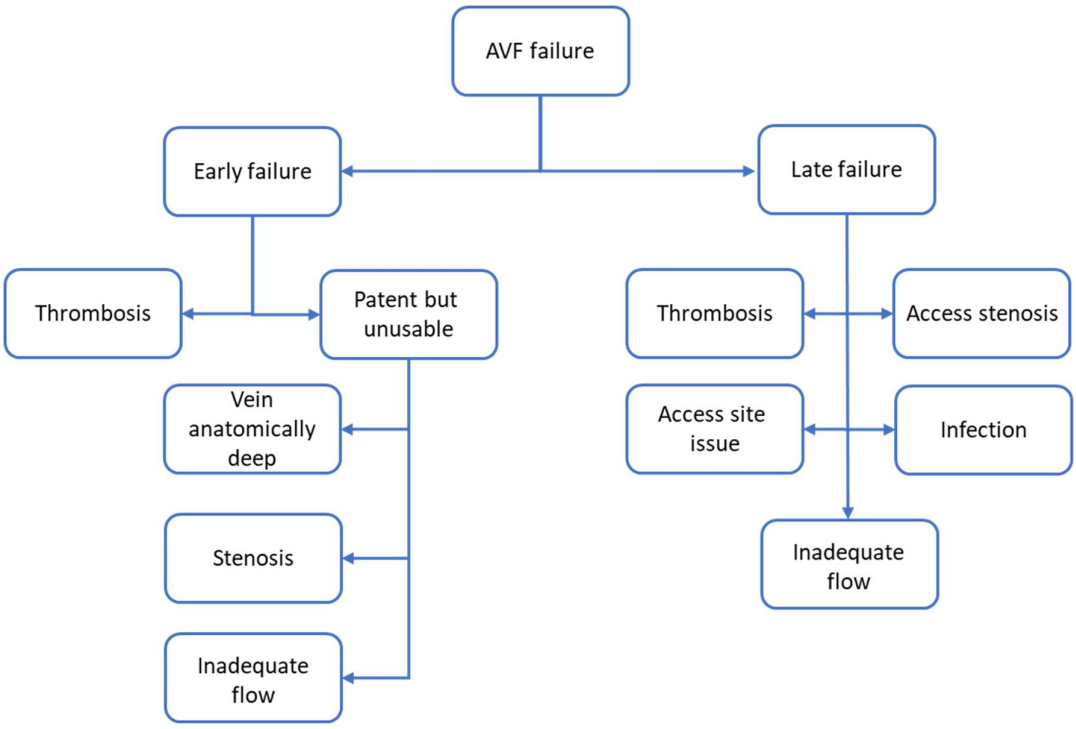


Figure 1.5: Fistula failure modalities

Early failure occurs prior to fistula utilisation, and typically arises within 6 weeks following fistula creation. Generally, there are 2 categories of early failure – thrombosis and non-maturation. Early failure has been attributed to several causes – surgical inexperience, poor preoperative vessel selection, usage of borderline vessels and a lack of surveillance and maintenance programmes [43].

1.3.1.3 Non-maturation

The term "non-maturation" refers to an AVF that is unsuitable for adequate haemodialysis after a minimum of 4 weeks and a maximum of 24 weeks from creation. Ever since the initial description of AVF in the 1960s, it has been accepted that 10-30% of fistulae will fail to mature. This is the "Achilles heel" of autogenous fistulae. Recently, other authors have reported an increase in fistula maturation failure, with a failure to mature rate of 24-60% [44–48]. The reasons for this are likely multifactorial: an aging population requiring dialysis with a greater burden of disease; better standardised reporting according to accepted conventions and a greater drive to create fistulae in patients despite suboptimal anatomy. Furthermore, there has been selection bias by some

authors reporting access results whereby fistulae experiencing primary failure and subsequent abandonment have been omitted from the data analysis, thereby portraying overly optimistic patency results.

The classical clinical presentation of a non-maturing AVF is either a thrombosed AVF or one that fails to increase in diameter or flow as would be expected. Clinical predictors of AVF maturation include size of vessels, site of fistula, surgeon-specific factors, female gender, ethnicity, diabetes and peripheral vascular disease [48]. On a practical level, only these first three factors are modifiable.

Attempts have been made to develop clinical scoring systems to quantify the risk of fistula non-maturation (FTM) to guide the surgeon's access management strategy. Lok et al [48] took into account the following four characteristics: age greater than 65, ethnicity, ischaemic heart disease, peripheral vascular disease to produce the following prediction score, with each variable scoring 1 if positive:

$$3 + 2 \times (age \geq 65) + 3 \times (Peripheral\ vascular\ disease) + 2.5 \times (Coronary\ artery\ disease) - 3 \times (white)$$

The resultant scores range from 0-10.5 and stratifies patients into four risk categories: low (<2.0; FTM 24%), moderate (2.0-3.0; FTM 34%), high (3.1-7.9; FTM 50%) and very high (>8.0; FTM 69%). Ultimately the aim was to guide decision making for optimal access creation, optimising resource allocation while reducing costs associated with repeated interventions or further access creation. The basis of Lok's scoring system was a relatively small cohort of 422 patients with fistulae created in a single Canadian institution which might solely reflect centre surgical outcomes. In her discussion, she also concedes that Afro-Caribbean patients made up less than 10% of the cohort, while other ethnicities made up 26% of the cohort; both these populations had higher rates of non-maturation. While her sample cohort appeared to be heterogenous, further clarity and characterisation with regards to ethnicity in the "other ethnicities" group would have been instructive. Another criticism is that even for patients deemed to be "low risk", the predicted FTM rate is 24% which seems inordinately high. Subsequent application of this scoring system has found limited value in predicting successful AVF use [44,47].

Surgical and endovascular interventions of non-maturing AVFs were examined in a systematic review by Voormolen et el, which has shown an overall fistula salvage rate of 86%, with 1 year primary patency of 51% and 1 year secondary patency of 76% [49]. Patients with preoperative clinical or haemodynamic risk factors had increased risk of fistula non-maturation (21% and 24%) respectively, but more significantly, individuals with low venous flow immediately post-surgery had a significant risk of fistula non-maturation (50%) [49].

1.3.1.4 Late failure

The majority of complications causing late fistula failure are a result of access stenosis [43]. This can be a consequence of neointimal hyperplasia, needling of the fistula by inexperienced dialysis staff or pre-existing proximal stenosis. Unrecognised stenosis eventually results in fistula thrombosis.

1.3.1.5 Interventions to salvage a failing fistula

Whilst both endovascular and surgical modalities are applicable for fistulae in all anatomical locations, their application can vary based on available clinical expertise and clinical situation. Endovascular techniques include percutaneous transluminal angioplasty of the arterial inflow or venous outflow stenoses, dilatation of juxta-anastomotic stenosis and balloon assisted maturation of non-dilating veins. A recent development has been the use of drug eluting balloons to treat stenoses, to reduce the rate of neointimal hyperplasia and consequently slow the onset of restenosis, but data remains scarce [50–52]. The long term primary assisted patency following percutaneous transluminal venoplasty is low [33]. Some authors have reported excellent outcomes following aggressive endovascular interventions to dilate stenotic lesions in non-maturing fistulae [24,53]. These techniques can cause intimal injury, and the resultant recurrent intimal hyperplasia and rapid restenosis necessitates multiple reinterventions to maintain patency [54]. Other studies, including one systematic review, have suggested that surgical revision of a failing fistula is superior to endovascular intervention [55,56].

1.3.2 Arteriovenous grafts

Arteriovenous grafts (AVGs) provide an intermediate option between AVFs and tunnelled catheters, permitting earlier cannulation compared to AVFs. AVGs are utilised when a venous limb is unavailable or deemed to be unsuitable for autogenous fistula creation, requiring the creation of a prosthetic extra-anatomical vascular access. The longevity and patency of AVGs are inferior to that of AVFs, with 1 year primary patency rates ranging from 40-60% [57]. Multiple interventions are often necessary to maintain access. With aggressive reintervention for graft thrombosis, 1 year secondary patency rates of 90% can be achieved [58]. In addition, as the AVG is composed of a synthetic material, the risk of infection is higher than that of autogenous fistulae; systemic bacteraemia rates of AVGs are 0.5-0.6 per 1000 dialysis days compared to 1.77 per 1000 dialysis days for CVCs and 0.3 per 1000 dialysis days for an AVF.

Up to 40-50% of incident haemodialysis patients commence dialysis without a functional AVF in place [59]. This is a result of a combination of late referral, primary access failure and acute presentation of renal failure (so-called “crashlanders”). A limitation of AVF deployment is the 6 to 8 week maturation “lag” from creation to first cannulation as well as the possibility of early AVF failure, which might necessitate the creation of a new autogenous fistula [60]. In contrast, standard AVGs require a delay of approximately 2 weeks from implantation to initial cannulation, necessitating temporary tunnelled line insertion. The recent introduction of early cannulation AVGs, which permit immediate needling, may eliminate this delay and consequently avoid the insertion of central venous catheters. Some groups have advocated placement of early cannulation grafts as a means to avoid central venous catheters, contending that this strategy reduced bacteraemia and mortality in patients requiring urgent vascular access [61,62].

1.3.3 Central venous catheters

Central venous catheters (CVC, Figure 1.6) appear to be the modality of necessity for initiation of haemodialysis. Among incident patients in the International Dialysis outcomes and Practice Patterns (DOPPS) study, more that 70% of haemodialysis patients initiated therapy via CVC [63]. The increased utilisation of central venous catheters parallels the growth of patients requiring urgent renal replacement therapy. Several

studies have confirmed that patients are more likely to prefer the original dialysis modality which is used during initiation of haemodialysis; other studies have confirmed that patients who dialyse via CVC are less likely to be amenable to switch to another haemodialysis modality, despite a detrimental effect to adjusted mortality [64,65].

Figure 1.6: Double lumen haemodialysis catheter

Dialysis via CVC carries a higher mortality and an increased risk of septicaemia, endocarditis and abscess formation [66]. The latest generation of tunnelled haemodialysis catheters are larger in diameter when compared to earlier generations, enabling greater blood flow rates, but also likely play a role in the development of symptomatic central venous stenosis [67]. Repeated CVC insertion or prolonged usage can lead to central venous stenosis and obstruction, which are not only challenging to treat but also jeopardise future upper limb access [68].

1.3.4 Complications associated with vascular access creation

1.3.4.1 Infection

One of the leading causes of death in adult patients with chronic kidney disease stage 5 is infection, which can be related to the type of vascular access in use. Rates of infections range from 2-3% in native fistulae, 11-35% in arteriovenous grafts and 20-50% in central venous catheters [69,70].

Arteriovenous grafts have a greater rate of infection than autogenous fistulae, and often requires surgical removal of infected graft material combined with antibiotic therapy for complete resolution. Catheter-related sepsis is a serious complication; Saad et al report that rates between centres vary from 1.3 to 5.5 episodes per 1000 catheter days [70].

1.3.4.2 Steal syndrome

Many complications are associated with AVF/AVG creation, but the most disabling and potentially damaging complication is a steal syndrome. Creation of an arteriovenous fistula or arteriovenous graft introduces an alternative low resistance pathway for blood to flow in preference to the usual high resistance arterial route, resulting in a portion of blood being diverted through the AVF/AVG. This non-anatomic shunt results in reduced distal arterial flow and consequently impacts distal perfusion. In the literature, multiple terms have used to describe this phenomenon: “steal syndrome”, “arteriovenous access ischaemic steal (AVAIS)”, “dialysis access steal syndrome (DASS)”, “haemodialysis access-induced distal ischaemia (HAIDI)”, “access-related ischaemia”, vascular access associated hand ischaemia”, “vascular access induced steal” and “distal hypoperfusion ischaemia syndrome” [71,72].

Present literature suggests that steal syndrome develops in 1 – 10% of patients with an AV fistula [73–76]. There is wide variation in the literature in the threshold for reporting steal phenomena, making comparisons between studies difficult. Classification of steal can be seen in Table 1.2 [75,77]. It can encompass a spectrum of symptoms from cold extremities, numbness, hand claudication, to rest pain and tissue loss (Figure 1.7 [71]), with intervention unnecessary in the mildest forms, whereas severe steal syndrome is debilitating and potentially limb-threatening and mandates surgical revision or ligation of the AVF/AVG. Several scoring systems to discriminate the severity of steal syndrome have been suggested in previous studies, but none of them have been widely used. Steal syndrome can theoretically be assessed with reasonable accuracy by measuring the Digital Brachial Pressure Index [78], but again, this approach has not gained widespread acceptance. Duplex ultrasound can also be used as a non-invasive modality to evaluate the vasculature of the arm and hand and to measure flow velocities, but this requires highly-trained vascular scientists.

Stage	Symptoms
0	Asymptomatic
I	Pale/blue and or cold hands without pain (steal phenomenon)
II	Pain on exertion and/or during haemodialysis
III	Rest pain
IV	Tissue loss – ulcers/necrosis/gangrene

Table 1.2: Classification of Steal syndrome

Pre-existing diabetes, female gender and the position of AVF created are independent risk factors for developing steal syndrome [79]. Generally, the more proximal the fistula, the greater the risk of steal syndrome. In addition, any patient with arterial occlusive disease is potentially at risk. The highest risk is seen in patients with an antecubital AVF i.e. brachiocephalic (BCF) or brachiobasilic (BBF) fistulae; up to 50% of patients in some studies, compared to 5-8% in all upper limb AVFs [78]. An alternative technique that may reduce the risk of developing steal syndrome in the group of patients undergoing placement of elbow fistula is to anastomose the vein to the proximal radial artery or ulnar artery, just distal to the brachial artery bifurcation. This technique, theoretically, will only 'steal' blood from one artery; i.e. the radial artery if the anastomosis is created on the proximal radial artery, maintaining blood flow through the ulnar arterial system.

Recent studies have suggested that using the proximal radial or ulnar artery as inflow reduces the risk of developing steal syndrome to as low as 0% to 3% [80–82]. The site of arterial inflow of an elbow AFF is therefore a potentially significant factor in causing steal syndrome. However, no current randomised controlled trial tests this hypothesis.

Figure 1.7: Ulcers on dorsal aspect of little finger secondary to ischaemic steal

A rare but potentially devastating complication of steal is ischaemic monomelic neuropathy. This is caused by a reduction of blood flow in the vasa nervorum because of steal phenomenon, predominantly in uraemic diabetics with pre-existing neuropathy. This results in severe sensorimotor dysfunction of the ulnar, median and radial nerves without obvious tissue loss. Symptoms often occur immediately after access creation, and if the ischaemia is not immediately reversed, irreversible neurological damage can occur.

Several modalities for the treatment of steal syndrome exist (Figure 1.8; modified from the ESVS Vascular Access Clinical Practice Guidelines [22]) . Endovascular treatment

of proximal arterial anastomosis can improve the distal arterial flow and consequently reduce distal ischemia. Open techniques to reduce the venous outflow include banding, plication of the venous segment with sutures, application of metallic clips just distal to the anastomosis or interposition of a narrow calibre PTFE graft. However, the degree by which the fistula is narrowed can prove to be unpredictable and therefore intra-operative digital perfusion by means of pulse oximetry, digital photoplethysmography or duplex ultrasound should be undertaken [74,83].

The DRIL (distal revascularisation with interval ligation) procedure can also be considered [84–86]. For this technique, the brachial artery just distal to the AV fistula is ligated to prevent backflow from the distal artery. A bypass graft from the proximal brachial artery to the distal ligated artery is then fashioned. Similarly, the revision using distal inflow (RUDI) procedure can be used [74,87–89]. This procedure involves ligating the AV anastomosis and revising the arterial inflow to a more distal source either with an interposition graft or by direct anastomosis. Ligation of the AV fistula is also a viable treatment, albeit a decision that should be considered as a last resort.

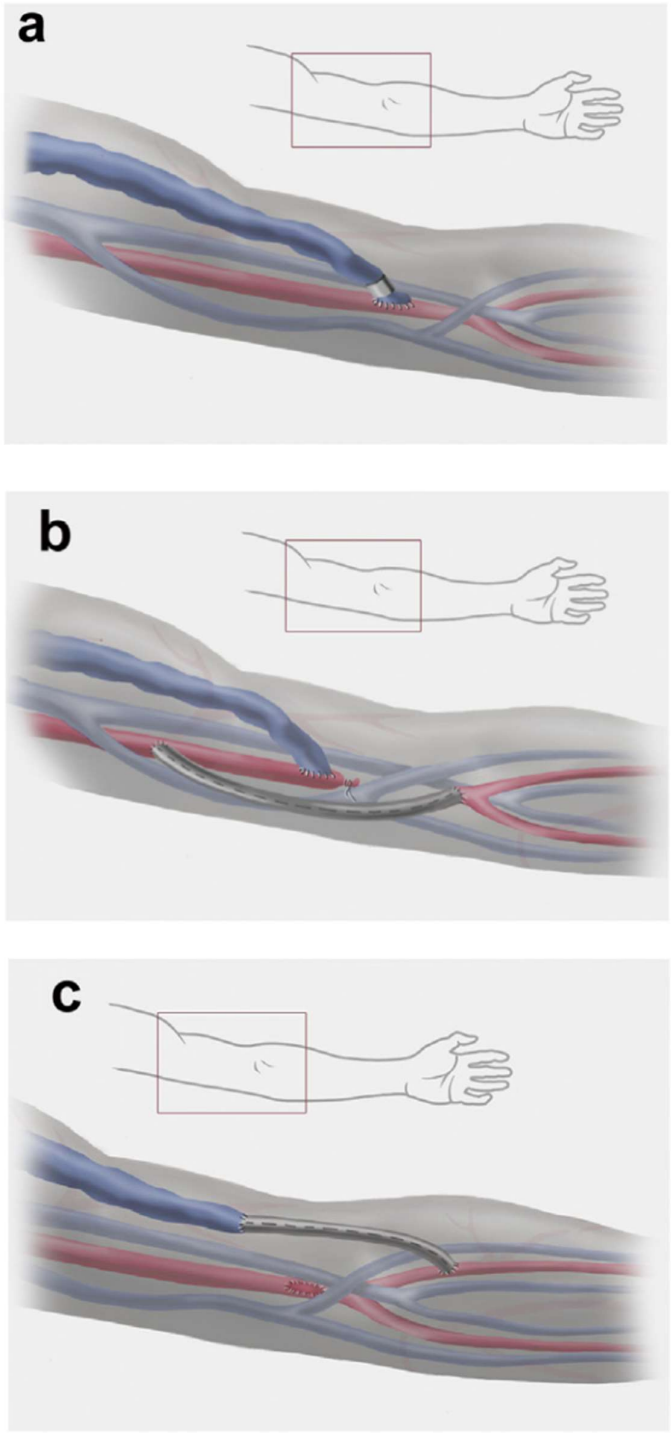


Figure 1.8: Surgical techniques for the treatment of steal syndrome

(A) Flow reduction by banding of the venous component just proximal to the anastomosis (B) DRIL procedure (C) RUDI procedure

1.3.4.3 Aneurysm formation

An aneurysm is a localised, pathological dilatation of the wall of a blood vessel. Aneurysmal dilatation may develop in an autogenous AVF over the course of many years (Figure 1.9). These develop as a result of repeated cannulations and vessel trauma along the length of the AVF, resulting in expansion of the autogenous AVF lumen. Needling technique also plays a part in aneurysm formation; buttonhole needling is associated with lower rates of aneurysm formation as compared to the rope-ladder or area puncture techniques [90–92]. Repeated needling results in multiple fibrotic scars in the vessel wall, which can expand over time leaving localised aneurysmal areas. Similarly, repeated localised punctures in prosthetic grafts can result in pseudoaneurysm formation. Whilst an aneurysmal AV access may raise concern from dialysis nursing staff, as long as the access remains functional for dialysis and the dilatation does not rapidly enlarge, no intervention is required. Indications for intervention include compromise of the overlying skin or intraluminal thrombus compromising dialysis [76,93]. Treatment of aneurysmal AVFs involve either ligation, plication, or creation of an end-to-end anastomosis by resecting the redundant aneurysmal segment.

Figure 1.9: Multiple aneurysms from repeated needling of a right radiocephalic fistula

1.3.4.4 Central venous stenosis

Use of central venous catheters can damage the central veins; one study by Kalman et al had found that 90% of patients with central vein stenosis had a prior central venous catheter insertion [94].

Treatment of central venous stenosis and occlusion (CVSO) is governed by the patient's symptoms. Incidentally detected asymptomatic stenoses should not be treated as these lesions can remain quiescent or even regress given time [95]. Conversely, angioplasty of such lesions can provoke rapid progression of stenosis.

For symptomatic patients, management is governed by several factors including symptoms severity, aetiology of CVSO and presence of an ipsilateral vascular access (Figure 1.10 and Figure 1.11 [96]). Haemodialysis patients with CVSO often present with a high-grade stenosis or functional occlusion, but without significant amounts of intraluminal thrombus (Figure 1.12 [96]). Angioplasty is often used, however recurrent stenosis is likely and therefore close clinical surveillance and repeated intervention are a mainstay of treatment [97–99].

Figure 1.10: Left ulnar-basilic fistula causing significant left arm lymphoedema

Also note the right infraclavicular pacemaker which would contribute to central venous stenosis as demonstrated by the prominent veins on the anterior chest wall

Figure 1.11: Post ligation of left ulnar basilic fistula

The picture demonstrates resolution of the left arm lymphoedema secondary to a arteriovenous fistula and central vein stenosis. Note that the patient was dialysing via an axillo-iliac graft

A

B

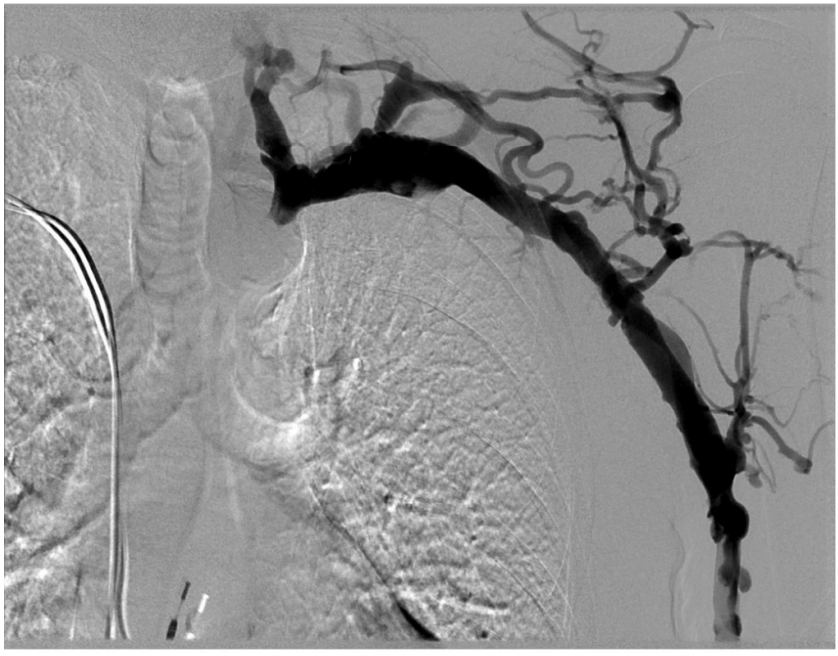


Figure 1.12: Venogram of the patient in Figure 1.10 demonstrating (A) Stenosis of the right subclavian vein (B) Occluded left brachiocephalic vein with distal collateralisation

1.3.4.5 High output cardiac failure

High output cardiac failure secondary to arteriovenous fistula formation, whilst exceedingly rare, is a well described phenomenon [76,100–102]. In contrast, its presence in relation to placement of a prosthetic graft is a less recognised phenomenon with limited reports [96,103]. Essentially, there is a marked reduction in systemic vascular resistance secondary to the functional vascular access, resulting in hypotension and fluid overload. Previous studies have shown that a vascular access flow/cardiac output (Qa/CO) ratio in excess of 30% place patients at risk of developing cardiac failure [102]. For individuals with autogenous fistulae, cardiac failure occurs insidiously. In contrast, for patients with prosthetic grafts, typically there is rapid onset of symptoms following insertion of the graft. With the advent of the Fistula First Initiative, elderly patients requiring prosthetic grafts tend to be cardiovascularly poor and with multiple previous attempts at autogenous fistula formation. Therefore, it is conceivable that a modest Qa from a graft could still precipitate catastrophic cardiac failure.

To mitigate the above risks, patients with pre-existing cardiac comorbidities should have preoperative echocardiograms and other investigations to determine their cardiac reserve. This may identify patients at high risk for development of cardiac failure and may even influence the decision to proceed with graft placement. It is important to consider the hemodynamic consequences when utilising central vessels for vascular access, particularly in the presence of underlying cardiac and vascular disease. In especially frail patients a tunnelled line might be the only option for vascular access.

1.4 Definition of Variables

Unless otherwise specified, all vascular access definitions were in accordance with the Society of Vascular Surgery/American Association of Vascular Surgery and North American Vascular Access Consortium [30,36]. Thus: immediate vascular access failure refers to an access that has a loss of bruit or thrill within 72 hours of creation; primary patency is defined as the interval from time of initial fistula placement until any intervention is performed to maintain or re-establish patency; and secondary patency is defined as the time of access placement until access abandonment. Proximal revision of a radiocephalic fistula that had failed immediately was considered as formation of a new primary fistula; proximal revision of a radiocephalic fistula in other circumstances was categorized as maintenance of secondary patency. Revascularisation using distal inflow (RUDI) procedure [77,88,89]; performed to ameliorate steal syndrome following creation of an antecubital fistula; was also considered as an intervention to maintain secondary patency.

To characterise the various grades of steal the grading system proposed by Padberg et el was used and this is detailed in Section 1.3.4.2 and Table 1.2 [76]. As mentioned above, there is no consensus in reporting standards for steal syndrome in the current literature, making comparisons between studies difficult.

A fistula was deemed matured if it sustained dialysis for at least three consecutive sessions [104]. This was based on previous published work in our unit and has been maintained throughout this thesis for consistency. A common accepted definition for a matured fistula is one that sustains six consecutive episodes of dialysis.

1.5 Scope of the thesis

As dialysis access procedures become increasingly complex, identification and management of complications have become a significant challenge. Current gaps in the literature include:

1. The relationship between brachial, pre- and post-operative digital pressure and the derivative digital brachial pressure index (DBPI) and symptomatic steal
2. The relationship between fistula flow rate and steal severity
3. The incidence of steal phenomena and steal syndrome in patients with antecubital fossa fistulae is uncertain and not clearly characterised in the literature
4. It is also unclear if utilising a distal arterial inflow (proximal radial/ulnar artery) in the antecubital fossa can improve reported symptoms of arteriovenous access associated steal compared to conventional fistulae utilising the brachial artery
5. The optimal autogenous access modality for elderly patients given their presumed limited life expectancy

For the purpose of this thesis, the vasculature of approximately 500 patients was analysed.

This thesis aims to examine three key questions:

1. Can digital finger pressure measurements and the derivative digital brachial pressure index help to identify patients at risk of arteriovenous access ischaemic steal?
2. Is it possible to reduce reported rates of steal and steal phenomena in autogenous fistulae located at the antecubital fossa by modifying the arterial inflow used?
3. Should elderly patients initiating haemodialysis be consigned to a more proximal antecubital fossa (brachial) fistula, or is a more distal wrist (radiocephalic) fistula an acceptable alternative?

These questions attempt to address the aforementioned gaps outlined above. Each question is examined, in turn, by the chapters following. All research was conducted at Cambridge University NHS Foundation Trust. Addenbrookes Hospital served as the primary base, and arteriovenous fistulae were created by two experienced consultant transplant surgeons and a team of senior trainees under consultant supervision.

Recruitment of patients to address the second question proved to be challenging and is discussed further in Chapter 3. Upon reflection, this was due to the success of our unit's radiocephalic fistula programme which naturally led to the third question – if radiocephalic fistulae should be offered to elderly patients with supposed limited life expectancy and this is addressed in Chapter 4.

2 The Role Of Digital Pressure And The Digital Brachial Pressure Index In The Identification Of Arteriovenous Access Ischaemic Steal (AVAIS)

2.1 Introduction

Haemodialysis (HD) via arteriovenous fistula (AVF) is the best modality for renal replacement therapy [20]. When compared to central venous dialysis catheters or arteriovenous grafts, AVFs have longer patency rates and have a reduced incidence of infection, stenosis and thrombosis [20]. As a consequence, mortality rates for patients dialysing via an AVF are lower compared to other dialysis modalities [105]; current guidelines advocate a "fistula first" approach in the provision of vascular access [20,106].

Arteriovenous fistulae are however not without drawbacks. One of the recognised complications of having an upper limb AVF is hand ischaemia which affects between 1-10% of patients [73–76]. This occurs as a consequence of preferential flow into the high flow, low resistance venous anastomosis at the expense of distal arterial circulation, resulting in hypoperfusion distal to the anastomosis. In theory, all patients with an AVF will have some degree of distal vascular compromise, albeit in the majority this compromise does not manifest clinically. In the remainder, distal hypoperfusion results in a constellation of symptoms, which, ranging from mild to more severe, include cold hands, paraesthesia, digital claudication, rest pain and gangrene (Figure 2.1). At its most severe, urgent surgical intervention is required. Individuals more likely to develop symptomatic arteriovenous access ischaemic steal (AVAIS) include those of female gender, diabetes mellitus, and age greater than 60 [73]. Furthermore, the incidence of AVAIS for patients with brachiocephalic fistulae is 5-10 fold greater than that of patients with radiocephalic fistulae [73–75,107].

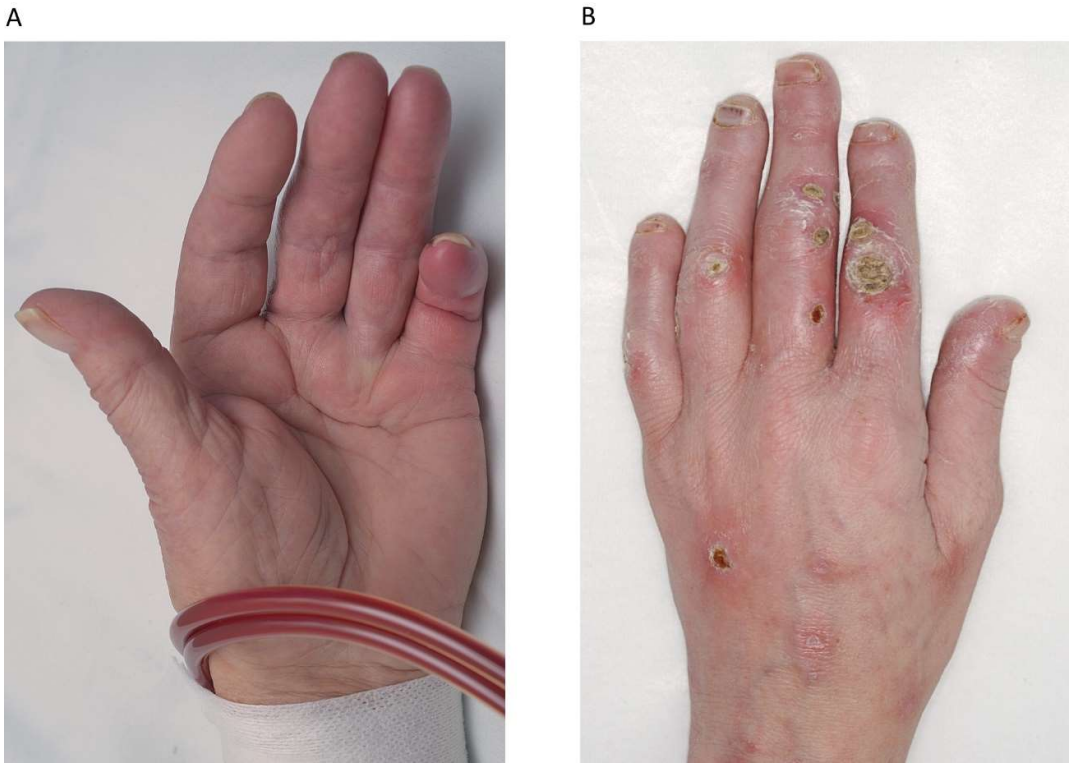


Figure 2.1: Complications of ischaemic steal

(A) digital cyanosis (B) tissue loss over proximal interphalangeal joints and ischaemic nail changes

Attempts have been made to grade AVAIS to facilitate comparison of severity, to aid in defining the necessity of various treatment options and allow evaluation of treatment efficacy following radiological or surgical interventions [77]. Scheltinga et al [71], refining work published by Tordoir [75], proposed grading ischaemic steal syndrome based on clinical symptoms, but this is not closely correlated with any objective measurements (Table 1.2). This closely mirrors the Fontaine score used to grade chronic lower limb ischaemia [108,109]. Van Hoek et al [110] used a patient orientated score, by means of a comprehensive visual analog scale to rate the severity and frequency of each of the five AVAIS symptoms i.e. coldness, paraesthesia, pain, weakness and cramps in the fistula hand.

Some studies have investigated the role of haemodynamic parameters as an objective tool to assist with the diagnosis of AVAIS and to assess the effectiveness of any intervention to ameliorate steal syndrome [78,111,112]. When comparing patients who had revision surgery for steal to those without, the Digital brachial pressure index (DBPI) was found to be significantly lower in the group of patients with severe steal requiring surgical intervention [78,113–115]. However, the role of DBPI in identifying patients with mild to moderate steal symptoms remains unclear.

The primary aim of this study was to establish, in HD patients with mature autogenous arteriovenous fistulae, if the digital (finger) pressure of the fistula arm differed significantly from that of the contralateral arm and if this had a direct relationship to symptoms experienced. The secondary objective was to investigate the relationship between fistula site and resultant digital pressure and DBPI.

2.2 Terminology and definitions

Current published literature uses several terms to describe steal phenomenon. Dialysis associated steal syndrome (DASS), haemodialysis access induced distal ischaemia (HAIDI), access-related ischaemia (ARI), vascular access associated hand ischaemia (VAAHI) have been used interchangeably in different publications [72]. A recent consensus document has suggested that arteriovenous access ischaemic steal (AVAIS) should be the preferred term [72]; to maintain clarity AVAIS is used throughout.

2.3 Methods

2.3.1 Patients

A prospective observational study was conducted in the Dialysis Unit at Addenbrooke's Hospital, Cambridge, from October 2011 to February 2012. Adult patients on long-term haemodialysis for end stage renal failure, dialysing via a functional upper limb autogenous arteriovenous fistula were recruited. To be considered functional, fistulae had to be used for at least three consecutive haemodialysis sessions [104].

The Addenbrooke's Dialysis Unit accommodates 134 haemodialysis patients. 110 patients had functional upper limb AV fistulae, of which 107 patients consented to participate in the study. A separate 23 patients received renal replacement therapy via central venous catheter and one patient dialysed via arteriovenous graft; these patients were excluded from the study. One patient had no signs or symptoms of circulatory compromise despite having an undetectable digital pressure. This patient was excluded from subsequent statistical analyses.

Haemodynamic parameters measured in each patient included brachial (BP) and digital (DP) pressures, from which the Digital Brachial Pressure Index (DBPI) was derived. Clinical AVAIS was graded using two methods: an Objective Score where examination of fistula and non-fistula hands were carried out by the investigator; and the Steal Symptom Score reported by dialysis patients using a visual analog scale as previously described by Van Hoek et. al [110].

2.3.2 Ethical approval

Ethical approval was granted by the London (East) Research Ethics Committee, REC 11/LO/1352 {Appendix 7.1 Ethical approval (Chapter 2)}.

2.3.3 Relevant medical history

Relevant medical history was obtained from the patient and medical notes. History of diabetes mellitus, hypertension, ischemic heart disease, cerebrovascular, peripheral vascular disease, thromboembolism, smoking history, cause of renal failure, dialysis history, the use of anticoagulation therapy, β-blockers, ACE inhibitors, statins, insulin and steroids were recorded.

2.3.4 Digital and Brachial pressure

The systolic digital (DP) and brachial blood pressure (BP) were measured on the fistula and contra-lateral arm, and then re-measured on the fistula arm with the fistula manually occluded. Digital pressures were measured using a Huntleigh Diagnostics™ Dopplex Assist Range digital pressure machine (Huntleigh Healthcare Ltd, Wales, UK, Figure 2.2). Brachial pressure was measured using a standard blood pressure cuff. DBPI was calculated from the ratio of DP to BP.

Figure 2.2: Huntleigh Dopplex Assist digital pressure machine

2.3.5 Objective Score - Clinical Examination of Hand

Each patient was first assessed clinically to determine if there was a history suggestive of either ischaemic claudication or rest pain. Clinical examination included a complete upper-limb vascular and neurological assessment. Both fistula and non-fistula sides were examined for skin temperature, colour, altered sensation, small muscle wasting, impaired motor power, evidence of tissue loss and delayed capillary refill time.

2.3.6 Steal Symptom Score

All patients completed a questionnaire to score five common symptoms of steal syndrome, using a visual analogue scale as detailed in Hoek et al [110]. They were asked to rate five domains: the frequency and severity of cold hands, pain, altered sensation (numbness/paraesthesia), reduced strength and cramps.

The individual steal symptom score is then calculated using the following formula:

Frequency of symptom [0 (never) to 10 (always)] x Severity of symptom [0 (no complaints) to 10 (maximal complaints)]

Each symptom scores a maximum of 100. The total steal symptom score is the sum of the five symptoms scores, giving a maximum score of 500.

2.3.7 Fistula Volume Flow (FVF)

Fistula volume flow was measured by either Transonic Flow-QC® Monitor (Transonic Systems Inc, Ithaca, NY, USA, Figure 2.3) or Doppler on the SonoSite MicroMaxx® Ultrasound System (Fujifilm SonoSite Inc, Washington, USA), depending on the accessibility of the two appliances at the time of study. The Transonic system measures true delivered blood flow through dialysis tubing using “gold standard” transit-time ultrasound technology.

Using the SonoSite, cross-sectional fistula diameter is first measured on 2D function. Doppler is subsequently used to derive the time-averaged mean velocity (TAMV). Fistula volume flow is then calculated by multiplying TAMV to fistula diameter. The doppler measurement was performed by a single operator using the same transducer to minimise operator-dependent error.

Figure 2.3: Transonic Flow-QC® Monitor

2.3.8 Statistical Analysis

All analyses were performed with GraphPad Prism (v.5.03 GraphPad Software Inc, CA, USA) and MedCalc (v 18.10 MedCalc Software, Belgium). Digital pressures and DBPI of the fistula arm and contralateral arm were compared using paired t-test. The relationship between digital and brachial pressures, DBPI and the steal symptom score was evaluated using Pearson's correlation. The significance of categorical parameters in the clinical manifestation of steal syndrome were examined using the Mann-Whitney U test.

2.4 Results

2.4.1 Patients

Demographics, past medical history and cause of renal disease of the 106 dialysis patients with functional upper limb fistulae are detailed in Table 2.1. The median age of the study population was 76 years old (range 26 to 95 years), and 71.7% (n = 76) were male.

	Haemodialysis cohort (n = 106)
Age median, years (range)	76 (26-95)
Gender, male	76 (71.7)
Comorbidities	
Smoking history	27 current smokers (25.5) 62 ex-smokers (58.5) 17 non-smokers (16.0)
Diabetes	54 (50.9%; 6 Type 1 and 48 Type 2)
Hypertension	81 (76.4)
Ischaemic heart disease	43 (40.6)
Aetiology of chronic kidney disease	
Idiopathic	18 (17.0)
Diabetic nephropathy	17 (16.0)
Adult polycystic kidney disease	10 (9.4)
Hypertensive nephropathy	7 (6.6)
Renovascular disease	7 (6.6)
Glomerulonephritis	6 (5.7)
Other	41 (38.7)

Table 2.1: Demographic data

Categorical variables are presented as number (%)

The cohort was subdivided into 2 groups based on the position of their fistula (forearm or antecubital, Table 2.2). 82 patients had fistulae sited in their forearm and 24 had antecubital fossa fistulae. Of the 24 patients, seven were felt clinically to be at higher risk of steal syndrome at the time of surgery. For these patients, the decision was made to use either the proximal radial or ulnar artery just distal to the brachial bifurcation as arterial inflow. These seven individuals were excluded from any analyses comparing forearm to antecubital fistulae.

Type of access	Total (n = 106)
Forearm	**82 (77.4%)**
(Primary) Radiocephalic	48
(Primary) Ulnarbasilic	3
Radiocephalic revision (neoanastomosis)	29
Ulnarbasilic revision (neoanastomosis)	2
Antecubital fistula	**24 (22.6%)**
Brachiocephalic	14
Brachiobasilic	2
Brachiocephalic revision	1
Proximal radiocephalic	4
Proximal ulnarcephalic	2
Proximal ulnarbasilic	1

Table 2.2: Type of arteriovenous access

Fistulae in italics were sited in the antecubital fossa but were excluded from analyses comparing antecubital fistulae to forearm fistulae. This is due to concomitant blood flow in the other artery, which would potentially preserve perfusion to the hand.

2.4.2 Digital pressure (DP)

The digital pressures for the 106 patients can be seen in Figure 2.4. Digital pressures were normally distributed; mean DP of the fistula arm was 96mmHg (95% CI 88-104), whilst mean DP of the contralateral arm was 137mmHg (95% CI 129-145). The mean difference between the digital pressure of the contralateral and fistula arm was 41mmHg (95% CI 35-48).

Of note, digital pressure once the fistula was occluded closely mirrored that of the contralateral arm, and both these values closely mirrored that of the brachial pressure (Figure 2.4).

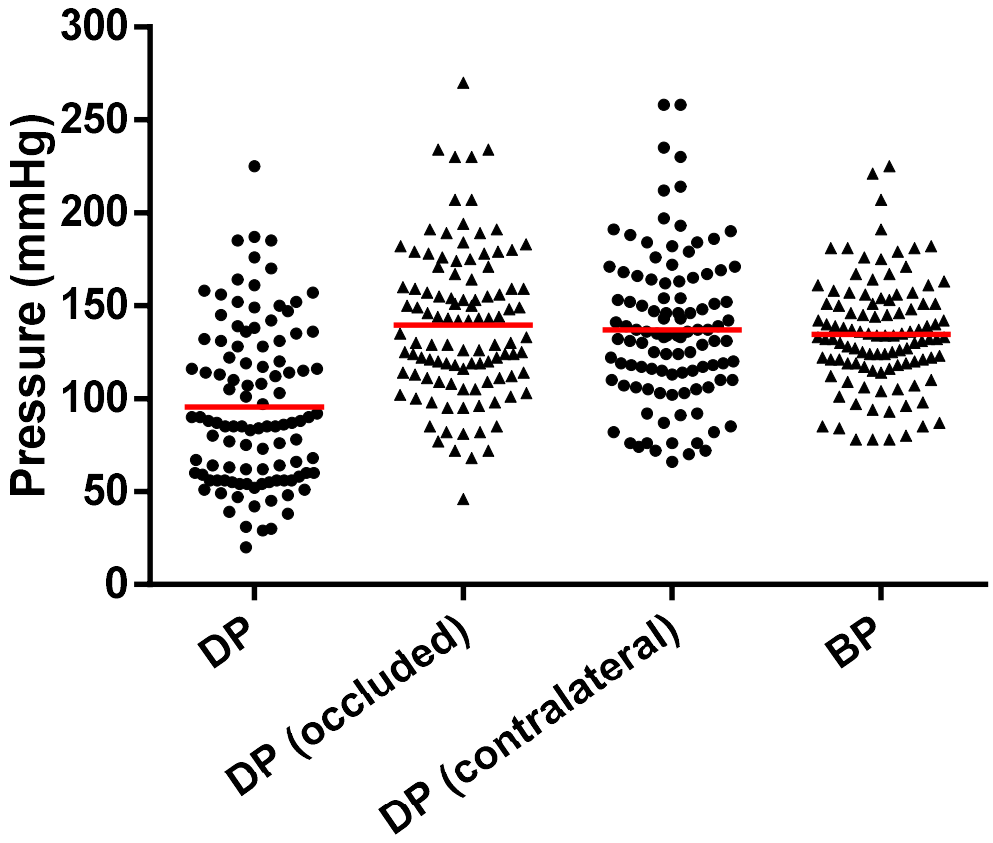


Figure 2.4: Scatter diagram of digital pressure (DP), DP when fistula occluded, DP of contralateral side and Brachial pressure (BP)

The red line denotes mean pressure of the cohort

There was a strong correlation between the digital pressures of the fistula arm and the contralateral side (r = 0.689, Figure 2.5); patients with low contralateral pressures tended to have lower digital pressures on the fistula side. This implies that for the majority of patients, distal vasculature and perfusion are similar in both arms.

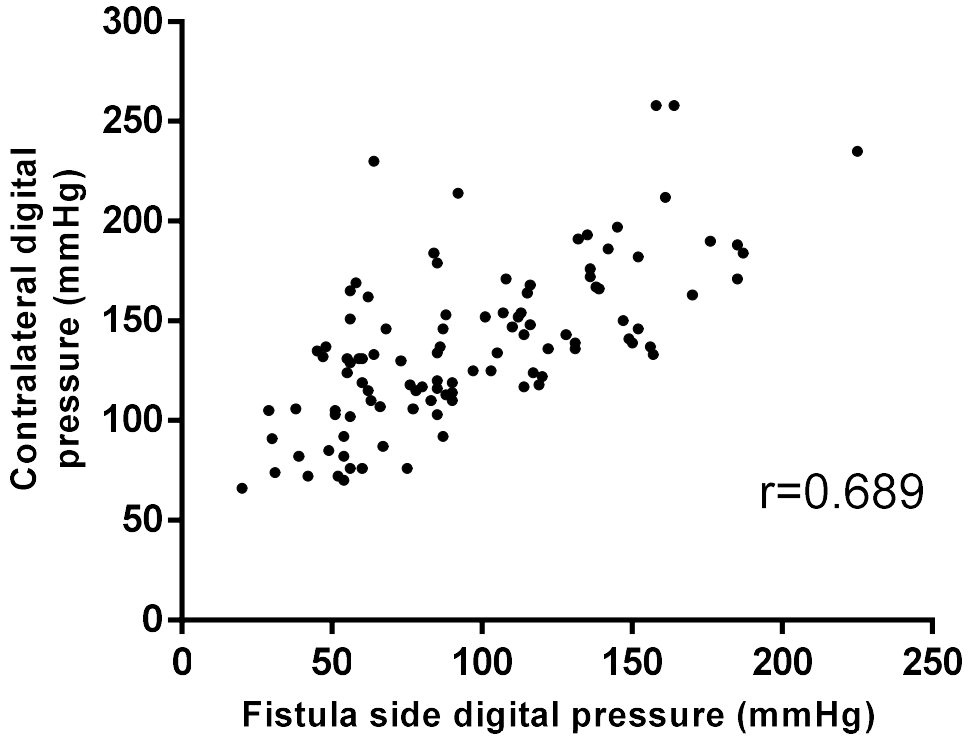


Figure 2.5: Correlation of digital pressure on fistula side vs contralateral side

There was also a strong correlation between the digital pressure in the contralateral arm and brachial artery pressure (r = 0.689, Pearson's correlation, Figure 2.6). In contrast, correlation between DP on the fistula side and brachial arterial pressure was less strong (r = 0.543, Pearson's correlation, Figure 2.7), reflecting variation in distal perfusion caused by the fistula.

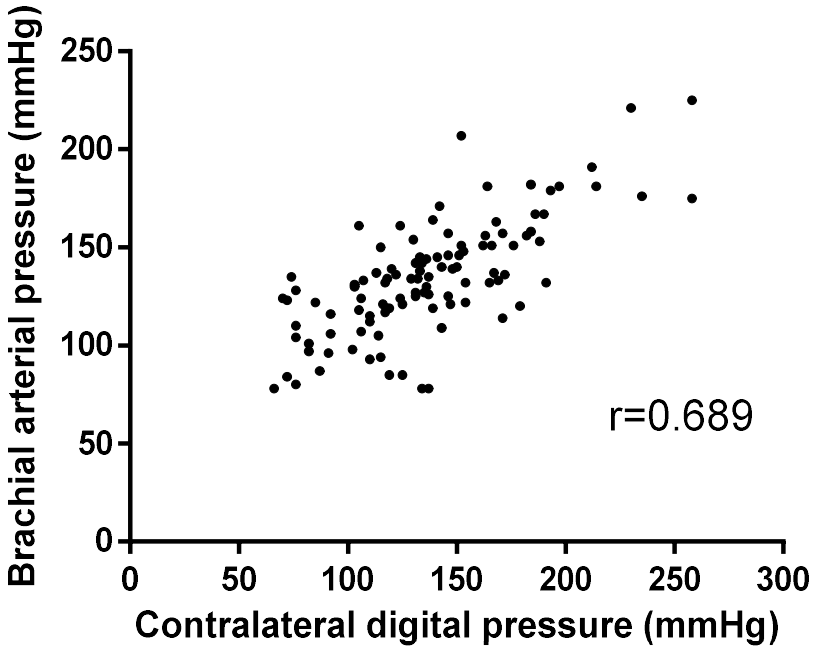


Figure 2.6: Correlation of contralateral digital pressure vs brachial artery pressure

There was a strong correlation between contralateral digital pressure and brachial artery pressure (r = 0.689, Pearson's correlation)

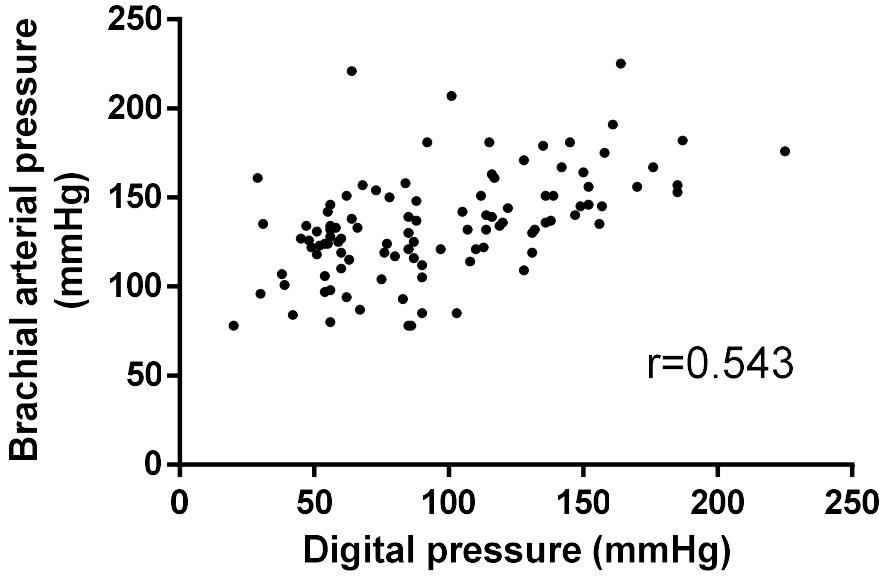


Figure 2.7: Correlation between digital pressure on the fistula side and brachial arterial pressure

2.4.3 Digital Brachial Pressure Index (DBPI)

The DBPI of all 106 patients is shown in Figure 2.8. DBPI of the fistula arm was significantly different from the contralateral arm ($P < 0.0001$, paired t-test). Similarly, DPBI of the fistula arm when the fistula was patent and when it was occluded was also significantly different ($P < 0.0001$, paired t-test). The mean DBPI gain when the fistula was occluded was 0.34. As expected, there was no significant difference between the DBPI when the fistula was occluded and that of the contralateral arm ($P = 0.1862$, paired t-test). There was also a strong correlation between these values ($r = 0.6801$, Pearson's correlation).

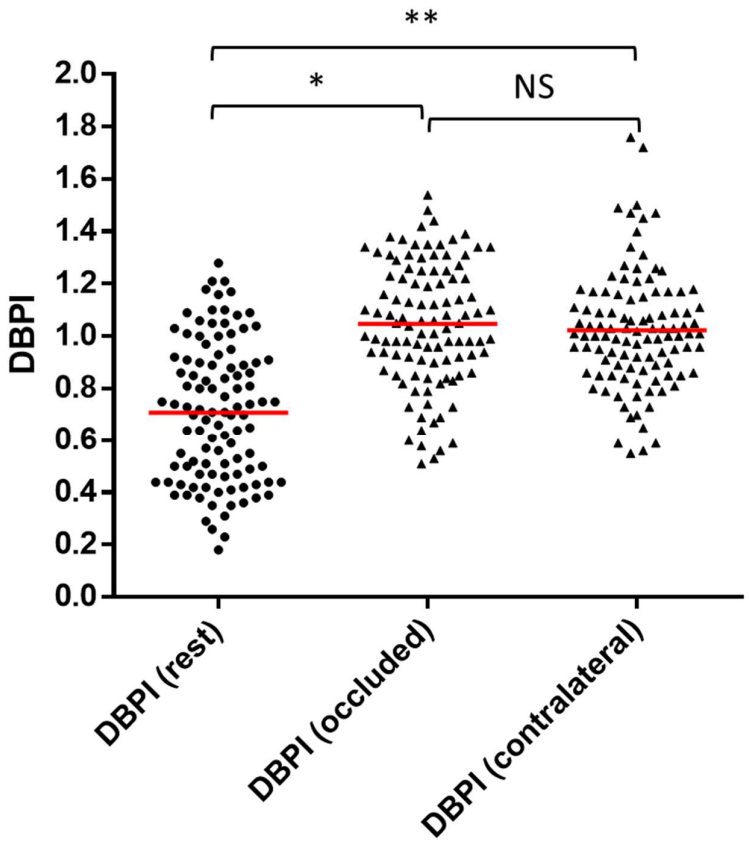


Figure 2.8: Scatter diagram comparing DBPI of fistula arm vs occluded vs contralateral arm

The red line denotes the mean DBPI of the cohort. * DBPI in the fistula arm was significantly different to the contralateral arm (paired t-test, P < 0.0001). ** DBPI of the fistula arm was significantly different when the fistula was patent and when it was occluded (paired t-test, P < 0.0001). NS, Not significant.

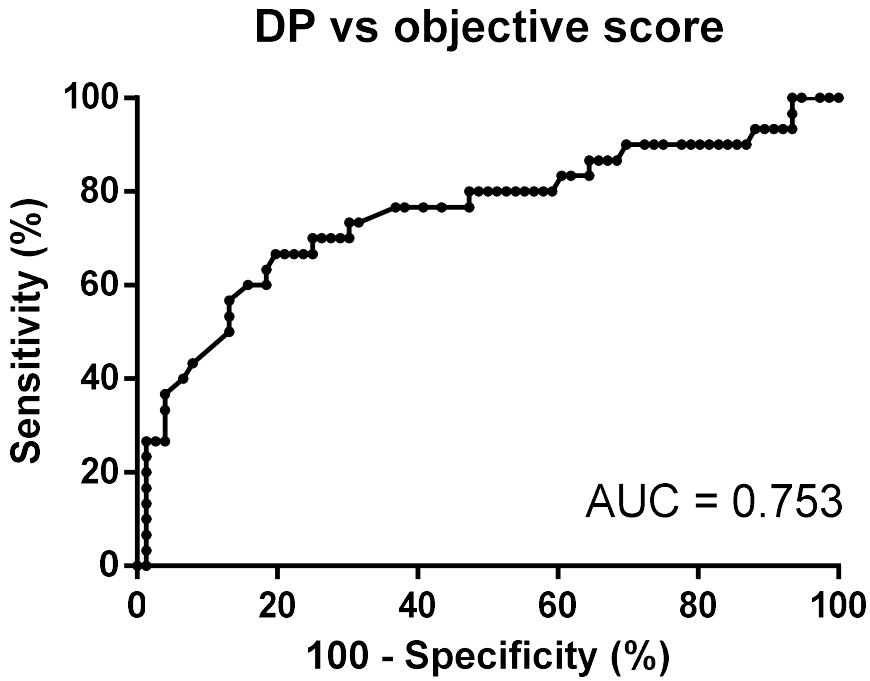
2.4.4 Objective Score

On clinical examination, 30 patients (28.3%) had at least 1 sign of steal syndrome. The most common sign detected was a difference in hand temperature between the fistula arm and contralateral limb (n = 21, 19.8%). Weakness was present in 11 patients, pallor occurred in 7 patients and 5 patients had more severe small muscle wasting in the fistula hand than the other hand. Capillary refill time was delayed in 3 patients. Twenty-two (20.8%) patients had cooler skin temperature in the fistula hand as compared to the non-fistula hand.

Using receiver operator characteristic (ROC) analysis (Figure 2.9 and Figure 2.10), the predictive ability of digital pressure for a positive clinical examination was estimated by calculating the area under the curve (AUC). The AUC was 0.753 (95% CI 0.640-0.868). The optimal cut off DP was calculated using Youden's ***J*** statistic (***J*** = Maximum {Sensitivity + Specificity -1}) [116]. The optimal cut off DP was 65mmHg, sensitivity was 66.7% (95% CI 47.2-82.7), specificity was 80.3% (95% CI 68.1-87.5), negative predictive value was 85.9% (95% CI 78.4 - 91.1). In comparison, at a cut off of 50mmHg, the sensitivity was 26.7% (95% CI 12.3-45.9), specificity was 96.1% (95% CI 88.9-99.2) and negative predictive value was 76.8% (95% CI 78.4 - 91.1).

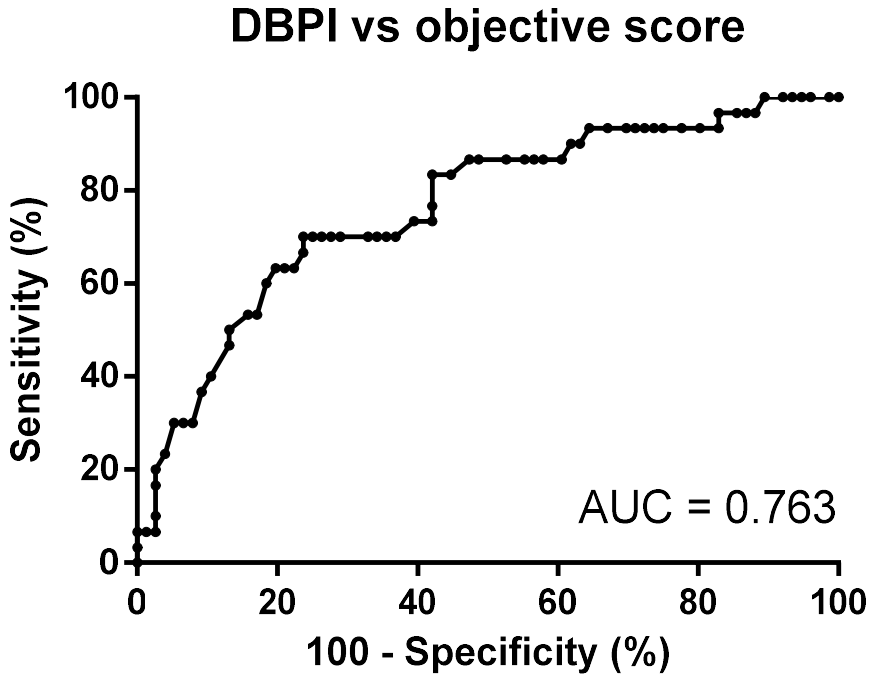
Similarly, when the ROC analysis was performed using DBPI instead of DP as a variable, the AUC was 0.763 (95% CI 0.661-0.865), and using Youden's ***J*** statistic the optimal cut off DBPI was calculated to be 0.57, which yielded a sensitivity of 70% (95% CI 50.6-85.3), specificity of 76.3% (95% CI 65.2-85.3) and negative predictive value of 86.6% (95% CI 78.6 - 91.9). In comparison, at a cut off DBPI of 0.50, the sensitivity was 60.0% (95% CI 40.6-77.3), specificity was 81.6% (95% CI 71.0-89.6%) and negative predictive value was 81.8% (95% CI 75.2 - 87.0).

Fourteen patients (13.2%) had 2 or more signs of steal syndrome; six patients had more than 2 signs of steal syndrome. One patient has critical ischaemia with dry gangrene, rest pain and impaired sensation of the index and middle fingers of the fistula hand.



Cutoff DP	Sensitivity%	95% CI	Specificity%	95% CI	Youden's J statistic
< 24.50	0	0.0% to 11.57%	98.68	92.89% to 99.97%	-0.013
< 30.50	6.667	0.8178% to 22.07%	98.68	92.89% to 99.97%	0.053
< 40.50	16.67	5.642% to 34.72%	98.68	92.89% to 99.97%	0.154
< 50.00	26.67	12.28% to 45.89%	96.05	88.89% to 99.18%	0.227
< 61.00	60	40.60% to 77.34%	84.21	74.04% to 91.57%	0.442
< 65.00	**66.67**	**47.19% to 82.71%**	**80.26**	**69.54% to 88.51%**	**0.469**
< 67.50	66.67	47.19% to 82.71%	77.63	66.62% to 86.40%	0.443
< 70.50	66.67	47.19% to 82.71%	76.32	65.18% to 85.32%	0.430
< 81.50	70	50.60% to 85.27%	69.74	58.13% to 79.75%	0.397
< 91.00	76.67	57.72% to 90.07%	52.63	40.84% to 64.21%	0.293
< 102.0	80	61.43% to 92.29%	50	38.30% to 61.70%	0.300
< 111.0	80	61.43% to 92.29%	43.42	32.08% to 55.29%	0.234
< 121.0	86.67	69.28% to 96.24%	32.89	22.54% to 44.63%	0.196

Figure 2.9: ROC curve of digital pressure vs clinical examination



Cutoff DBPI	Sensitivity%	95% CI	Specificity%	95% CI	Youden's J statistic
< 0.2050	3.333	0.08436% to 17.22%	100	95.26% to 100.0%	0.033
< 0.3000	6.667	0.8178% to 22.07%	97.37	90.81% to 99.68%	0.040
< 0.4050	30	14.73% to 49.40%	93.42	85.31% to 97.83%	0.234
< 0.5050	60	40.60% to 77.34%	81.58	71.03% to 89.55%	0.416
< 0.5250	63.33	43.86% to 80.07%	78.95	68.08% to 87.46%	0.423
< 0.5550	66.67	47.19% to 82.71%	76.32	65.18% to 85.32%	0.430
< 0.5650	**70**	**50.60% to 85.27%**	**76.32**	**65.18% to 85.32%**	**0.463**
< 0.5800	70	50.60% to 85.27%	75	63.74% to 84.23%	0.450
< 0.6000	70	50.60% to 85.27%	73.68	62.32% to 83.13%	0.437
< 0.7050	73.33	54.11% to 87.72%	60.53	48.65% to 71.56%	0.339
< 0.8050	86.67	69.28% to 96.24%	47.37	35.79% to 59.16%	0.340
< 0.9050	93.33	77.93% to 99.18%	32.89	22.54% to 44.63%	0.262

Figure 2.10: ROC curve of DBPI vs clinical examination

2.4.5 Steal Symptom Score

The distribution of reported scores can be seen in Figure 2.11. 30 patients reported no change (score = 0) in symptoms as a result of having a fistula. The median score in the cohort was 25. Categorical symptom scores are shown in Figure 2.12. The most common complaint by patients on the fistula hand was coldness, which accounted for 48.1% of patients (n = 51), followed by paraesthesia in 45.3%, cramps in 36.8%, weakness in 31.1% and pain in 17.9%. Symptoms were mild to moderate in the majority of cases, although 17.0% of patients (n = 18) had a total symptom score of more than 100 (Figure 2.11, median = 25). Coldness, cramps and paraesthesia was also experienced to a lesser degree in the non-fistula hands in 27.4%, 25.5% and 22.6% of patients respectively.

11 patients had digital pressures less than 50mmHg; all had a DBPI <0.6. When this group was compared against the rest of the cohort with digital pressure greater than 50mmHg, there was a significant difference in the Steal symptom score (P = 0.032, Mann-Whitney U test).

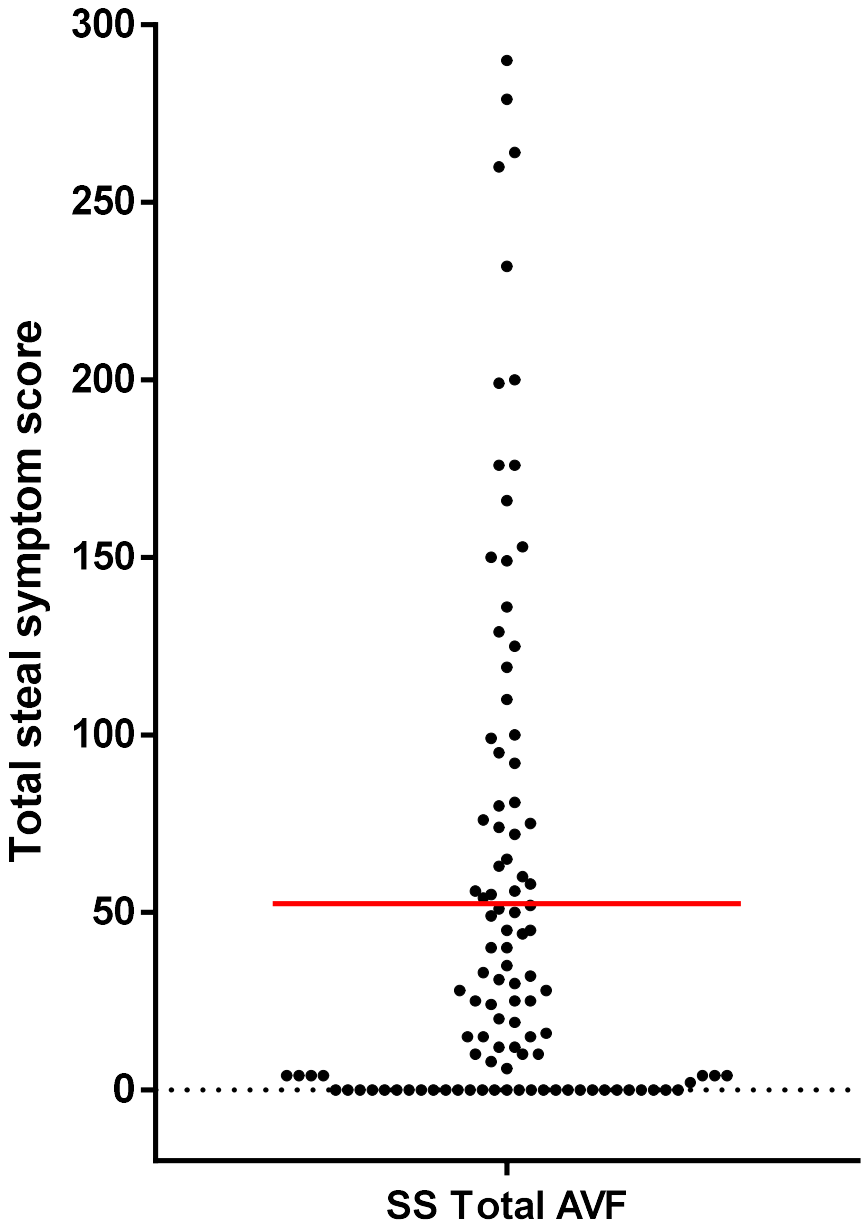


Figure 2.11: Scatter diagram of Steal symptom score distribution.

Red line denotes mean score. Score range from 0-500.

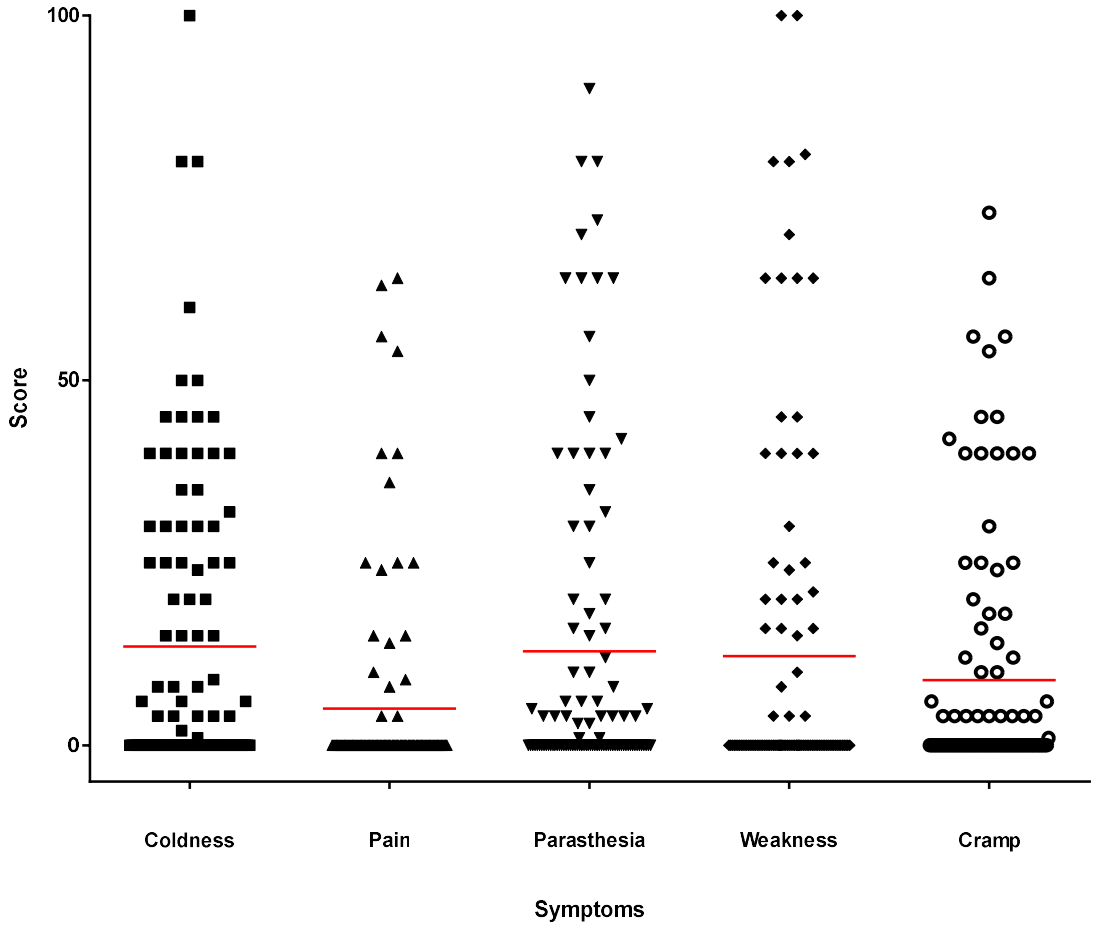


Figure 2.12:Categorical symptom score

Red line denotes mean score for each variable. Score range from 0-100

Sixteen patients had a contralateral pressure of <100mmHg, with a mean Steal symptom score of 96. When these patients' Steal symptom score was compared against the scores from patients with contralateral pressure ≥100mmHg (mean Steal symptom score 45), again there was a significant difference in the Steal symptom score (P = 0.011, Mann-Whitney U test, Figure 2.13). This suggests that patients with low systemic blood pressures will tend to have higher Steal symptom scores and will be more symptomatic.

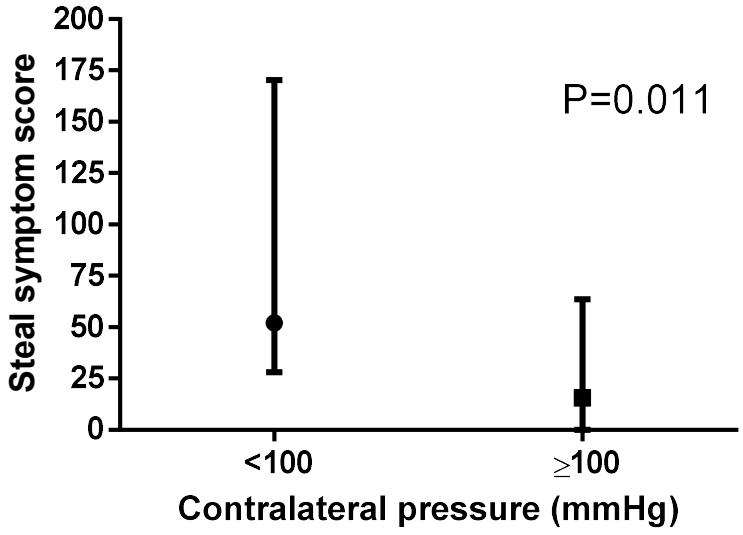


Figure 2.13: Comparison of Steal symptom scores for contralateral pressure <100 and ≥100 mmHg

Nevertheless, there was very poor correlation between the Steal symptom score and DP/DBPI, implying that a linear relationship does not exist (r = -0.154 and -0.109 respectively, Pearson's correlation, Figure 2.14).

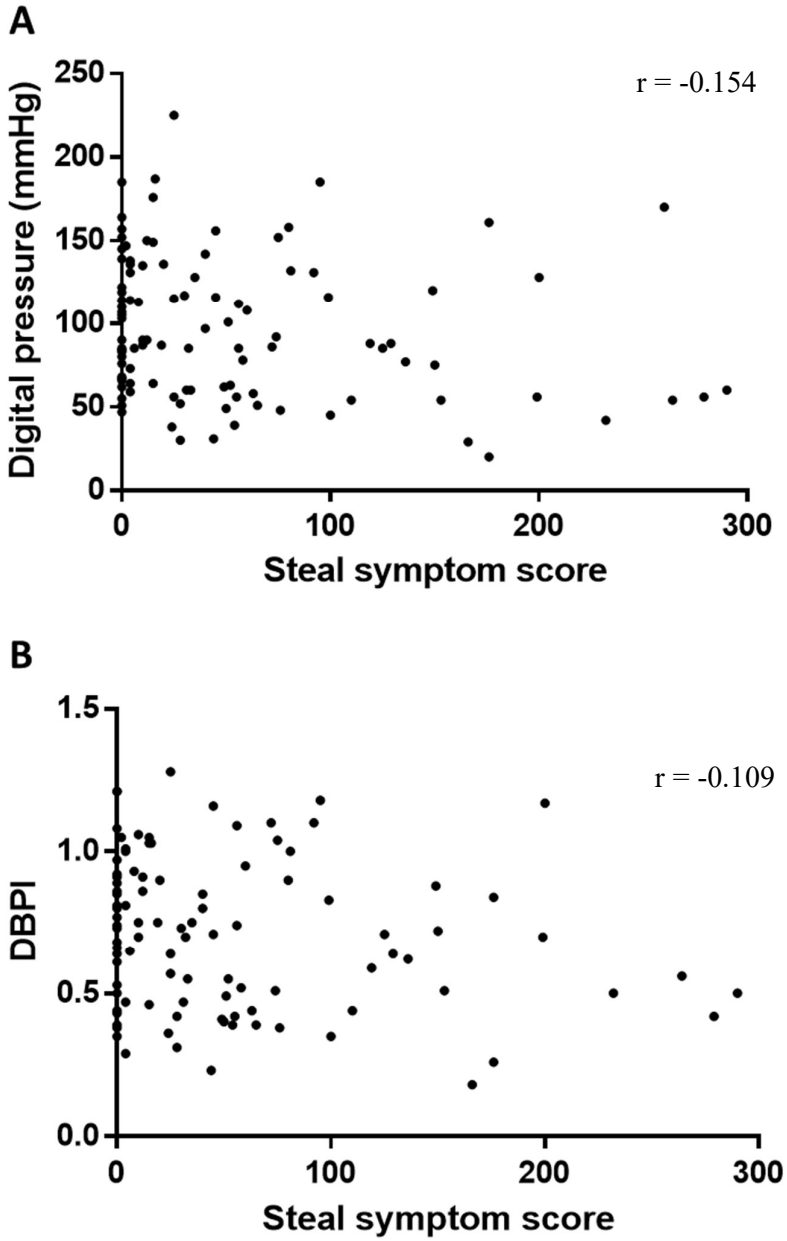


Figure 2.14 Correlation between Steal symptom score and fistula side (A) Digital pressure (B) DBPI

There was no linear correlation(A, r = -0.154; B, r = -0.109; Pearson's correlation).

2.4.6 Fistula Volume Flow

There was a significant difference in fistula volume flows depending on the site of the fistula ($P < 0.0001$, Mann-Whitney U test, Figure 2.15). Median flows for fistulae utilising the brachial artery were 1730mls/min (range 500-3680). In comparison, for fistulae created using the ulnar or radial arteries, median flow was 690 mls/min (range 210-2100).

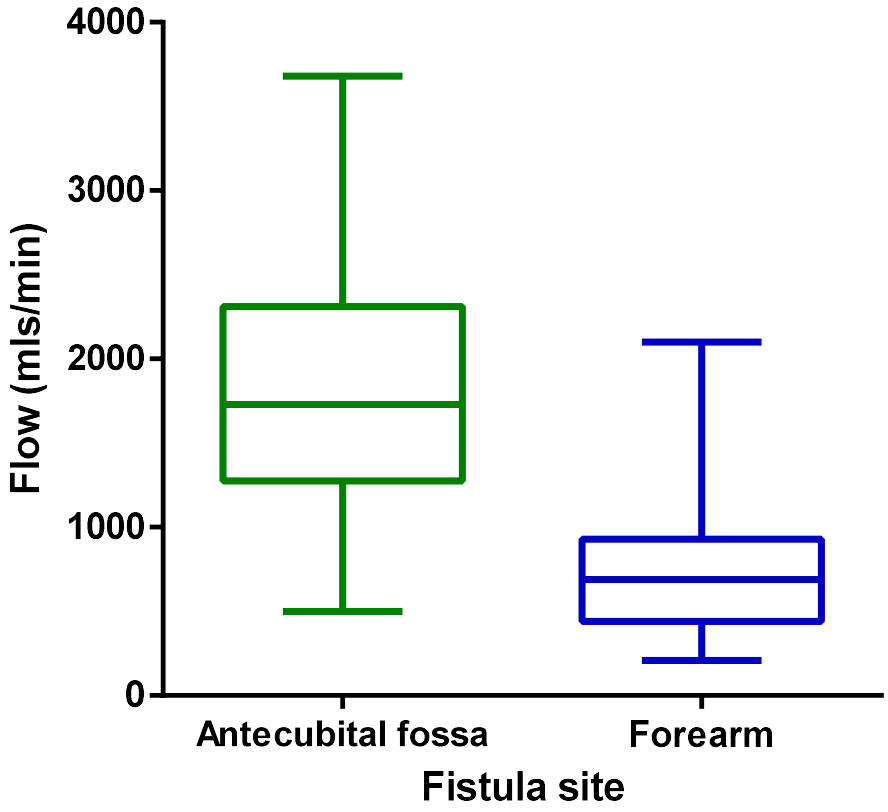


Figure 2.15: Box diagram comparing fistula flow volume between fistulae sited at the antecubital fossa and at the wrist

There was no linear correlation between DBPI and fistula volume flow; similarly, no linear correlation existed between DBPI and steal symptom score. DBPI was negatively correlated to objective score; The lower the DBPI, the higher the objective score observed; the correlation was weak ($P < 0.001$, correlation coefficient = -0.331). There was no association between steal symptom score and objective score ($P = 0.053$).

2.4.7 Fistula site

When the fistula site was considered (Figure 2.16), mean digital pressures of fistulae sited at the wrist, ACF and distal ACF were 99 mmHg (95% CI 90-108), 90 mmHg (95% CI 65-114) and 68 mmHg (95% CI 36-102) respectively. While there was a difference in mean digital pressure between these 3 groups, this was not statistically significant. There was a significant rise in digital pressure in each group when the fistula was occluded, and this was statistically significant in each case. Patients who had fistulae created in the in the distal ACF (utilising proximal radial / ulnar artery inflow) had the lowest mean digital pressure of the 3 groups. These individuals were deemed to be at high risk of steal due to pre-existing comorbidities and it is not surprising that this cohort's digital pressures were lower.

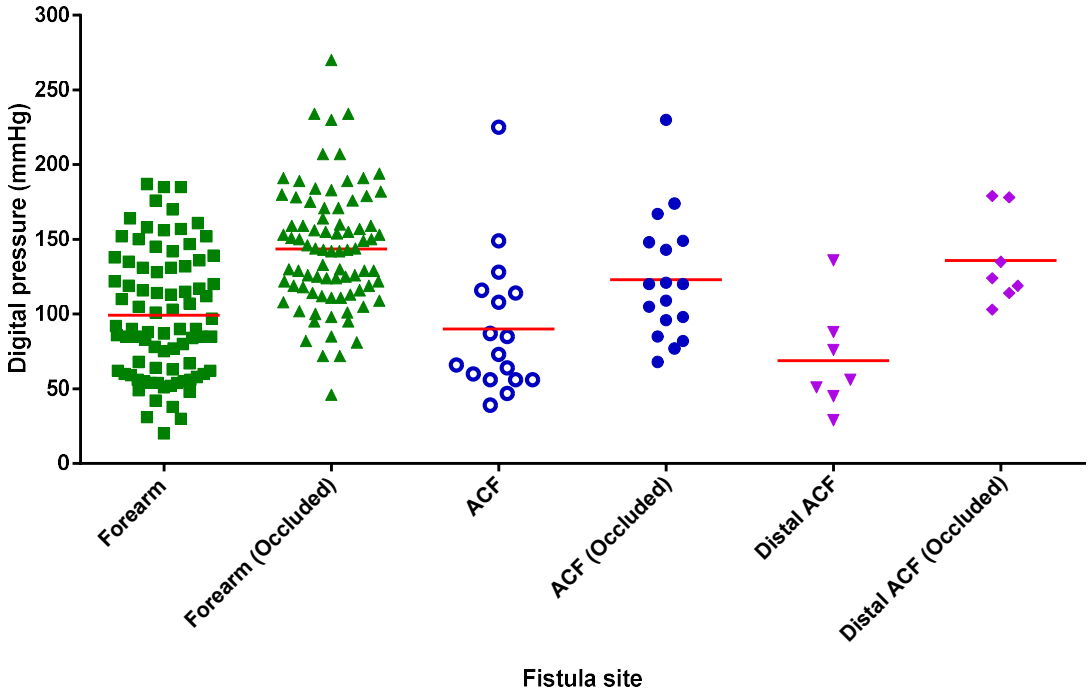


Figure 2.16: Digital pressure of fistulae sited at the wrist, antecubital fossa and distal antecubital fossa

ACF, antecubital fossa. Fistulae sited in the distal ACF are those that utilise proximal radial / ulnar artery inflow. The corresponding digital pressure when the fistula was occluded is displayed in the adjacent column in the same colour. The red line denotes the mean value of each cohort.

Similarly, when considering the DBPI of each cohort a similar picture is seen. All 3 cohorts have a mean DBPI of 1 when the fistula is occluded. Mean DBPI of fistulae sited at the wrist, ACF and distal ACF were 0.73 (95% CI 0.67-0.79), 0.70 (95% CI 0.56-0.84) and 0.51 (95% CI 0.27-0.76) respectively. Whilst the DBPI of patients with antecubital fossa fistulae (n = 17) were lower than that of those with forearm fistulae (n = 81), this was not significant (P = 0.669, unpaired t-test). The difference in DBPI between the fistula arm and contralateral side remained even within the subgroups.

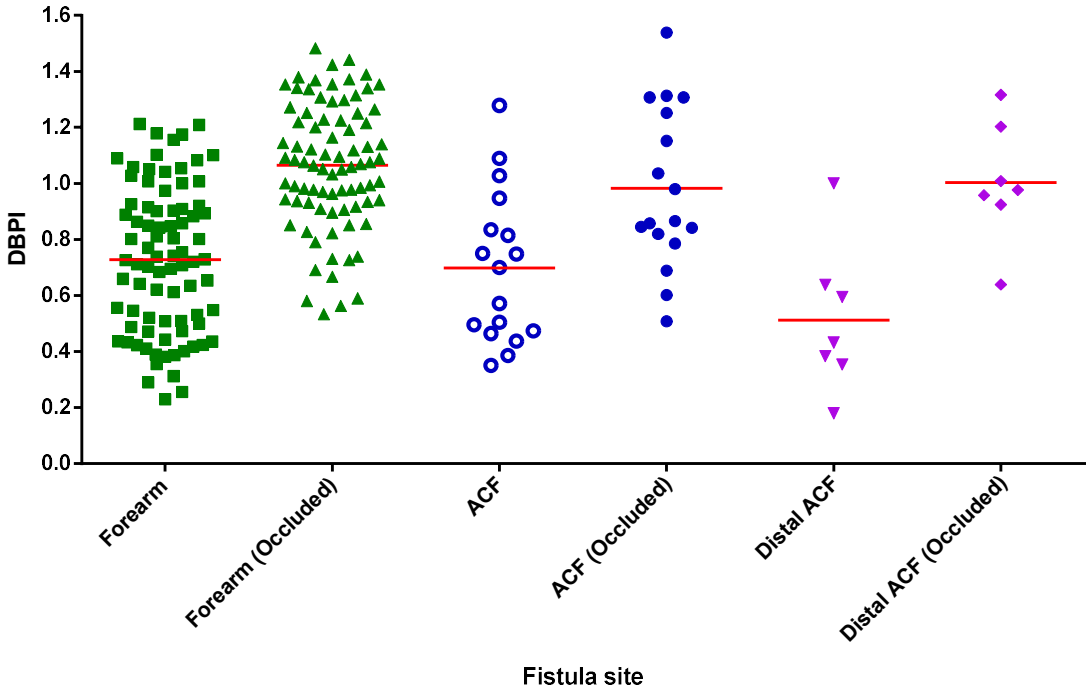


Figure 2.17: DBPI of fistulae sited at the forearm, antecubital fossa and distal antecubital fossa

ACF, antecubital fossa. Fistulae sited in the distal ACF are those that utilise proximal radial / ulnar artery inflow. The corresponding DBPI when the fistula was occluded is displayed in the adjacent column in the same colour. The red line denotes the mean value of each cohort.

2.5 Limitations

This prospective observational study was performed in a single institution cohort with a predominantly Caucasian demographic. During the study period, no patient developed critical hand ischaemia necessitating surgical intervention. Being an observational study, seven patients who were felt to be at greater risk of developing steal syndrome had had a proximal radial/ulnar artery to cephalic vein anastomosis created. These individuals might have developed more severe symptoms if a conventional brachiocephalic fistula had been created instead.

2.6 Discussion

In the vast majority of patients, digital pressures are reduced in the fistula arm, but upon occlusion of the fistula revert to pressures similar to that of the contralateral arm. More importantly, patients with low brachial pressures tended to have correspondingly lower absolute digital pressures, which is a phenomenon that has not been previously recognised. Only patients with markedly reduced digital pressures were symptomatic.

Identification of individuals at risk of developing arteriovenous access ischaemic steal remains a challenge. It can present as a spectrum of symptoms; whilst most individuals experience mild discomfort with a single symptom such as cold hands, a smaller proportion experience a constellation of debilitating symptoms. This study attempts to quantify the proportion of individuals experiencing both mild and severe symptoms and correlate their reported symptoms with objective measurements (DP/DBPI).

AVAIS is a problem experienced by a significant proportion of our cohort. Despite this, no individual with steal required surgical intervention. This can perhaps be attributed to the relatively modest cohort size. Another possible explanation might be that our cohort has a lower rate of distal arterial disease as compared to other populations. In mitigation, rates of smoking, diabetes and ischaemic heart disease were comparable to other published studies [113,117–119]. What remains unknown is the long term sequlae of AVAIS and whether individuals with moderate symptoms eventually progress to require surgical intervention.

This study demonstrates that the DP of the fistula arm when the fistula is occluded is closely correlated to that of the contralateral arm; this in turn suggests that the distal vasculatures appear similar. This implies that there is no clinical advantage in choosing the laterality of the fistula's position; for individuals who experience steal, formation of an identical fistula on the contralateral arm is equally likely to result in steal. Naturally, this is with the caveat that the underlying vasculature is similar with no arterial stenoses, venous outflow obstruction or previous line placement causing central venous stenosis. However, we recognise that positioning a fistula in the non-dominant arm is certainly more convenient for the patient.

A low preintervention DBPI suggests inherent peripheral small vessel arterial disease, leading to decreased perfusion of extremities. Small vessel disease also increases resistance to flow and therefore flow velocities are reduced. We submit that the inherent quality of vessels is a major determinant of the manifestation of signs of steal. Furthermore, the initiation of haemodialysis can result in systemic hypotension, exacerbating an already diminished hand perfusion. Strategies to reduce dialytic hypotension will possibly decrease symptoms associated with haemodialysis access-induced distal ischaemia [112].

We propose that recording preoperative digital pressures and DBPI may give an indication of the likelihood of a patient developing steal and therefore appropriate advice and counselling can be provided prior to the creation of an autogenous fistula. In individuals with existing low digital pressures an autogenous fistula might be relatively contraindicated. Postoperatively, our results show that, at least for our cohort, patients with a DP greater than 65mmHg or DBPI greater than 0.57 are unlikely to display clinical symptoms.

The steal symptom score utilised in this study was based on a hand ischaemia questionnaire developed by van Hoek et al [110], which found that mild to moderate symptoms of steal are common in patients dialysing via autogenous fistula and that this was more common in individuals dialysing via BCF as compared to those dialysing via

RCF (50% vs 12%). Disappointingly, there was poor correlation between the Steal symptoms score and DP / DBPI, implying that a linear relationship does not exist. The reason for this is probably due to the equal weight given to each of the five domains when practically the symptoms of pain and claudication represent a progression of symptom severity compared to coldness and paraesthesia. This makes it difficult to make any meaningful comparison between individuals with varying Steal symptoms scores. Classification using the Objective score, into the groups proposed in Table 1.2, proved to be far more useful.

Whilst there is certainly greater blood flow in an elbow versus distal wrist fistula, in our cohort there was no linear correlation between flow volumes and severity of steal. Similarly, Hoek et al [110], reported that higher access flows were not associated with greater steal symptoms. This is surprising as other published literature have suggested that DBPI is lower in patients with fistulae in the antecubital fossa [110]. Therefore, the manifestation of steal is probably multifactorial and a reflection of systemic hypotension, relatively increased fistula flow coupled with a poor-quality distal vasculature. At our institution, we pursue a policy of creating radiocephalic fistulae in preference to brachiocephalic fistulae and therefore any individual dialysing via a brachial fistula would generally have had exhausted all distal options.

Patients with low brachial pressures tended to have a correspondingly low digital pressure in both the fistula arm and contralateral arm (Figure 2.7). This poses a dilemma for the surgeon: creating a fistula in a hypotensive patient is more likely to exacerbate the problem and increase the probability of steal syndrome. A hypotensive patient's fistula is also less likely to mature [120].

In conclusion, digital pressures are universally reduced in the fistula arm when an AVF is created. There is a linear association between low fistula-arm DBPI and low DBPI in the contralateral arm, suggesting that measuring DBPI prior to vascular access surgery may be useful in identifying patients at risk of developing critical steal syndrome. It can be inferred that systemic hypotension following the initiation of haemodialysis can

exacerbate an already diminished hand perfusion and measures preventing hypotension during haemodialysis will likely improve symptoms associated with haemodialysis access-induced distal ischaemia [112]. Once identified, these patients at risk of AVAIS should undergo regular post-operative digital pressure measurements as part of departmental policy to ensure accurate monitoring and subsequent timely surgical intervention if required.

2.6.1 Novel Findings

This chapter has identified several results that have not been previously recognised in the literature:

Patients with low brachial pressures tended to have corresponding lower digital pressures (and tended to be more symptomatic). It also demonstrates that bilateral digital pressures are similar once the fistula is occluded. This is important as it suggests that, for patients that are symptomatic, placement of a similar fistula on the contralateral side is likely to result in comparable symptoms.

I have demonstrated that DP and DBPI can be used as a sensitive measure for detecting and predicting steal syndrome. I identify that a DP of <65mmHg or DBPI <0.57 is the optimal point at which a patient is likely to have a positive clinical examination for steal.

I establish that there is no linear relation between fistula flow rate and severity of steal.

3 RANDOMISED CONTROLLED TRIAL COMPARING THE INCIDENCE OF STEAL SYNDROME IN TWO TYPES OF ANTECUBITAL FOSSA ARTERIOVENOUS FISTULAE (STEAL TRIAL)

3.1 Introduction

There are multiple modalities of haemodialysis for patients with end stage renal failure. Examples include arteriovenous fistula, arteriovenous graft, indwelling central venous catheter as well as HeRO graft (hybrid graft / indwelling catheter). Arteriovenous fistulae (AVF) remain the preferred form of vascular access for long-term haemodialysis in patients with end-stage renal failure as they are associated with the lowest risk of complications, lowest need for interventions and best long-term patency [17,121]. Due to the rise in median ages of incident and prevalent haemodialysis patients, access-related ischaemia presents a significant problem in this cohort of patients.

The accepted strategy in creating an AVF in the upper limb is to start at a distal site and should that fail, to form an AVF at a more proximal site i.e. from wrist to forearm and subsequently to elbow. The rationale for creating fistulae in this fashion is that it preserves precious venous capital. The most common type of AVF is the radiocephalic AVF sited at the wrist. A more proximal AVF is often created as a primary procedure when there is poor vasculature in the distal forearm or as a secondary procedure when a wrist fistula has failed. Traditionally, the brachiocephalic fistula (BCF), which involves anastomosing the cephalic vein to the brachial artery, has been the most common type of AVF created in the antecubital fossa at the elbow level. Other common types of antecubital fossa arteriovenous fistula (AFF) include the brachio-basilic and brachio-median cubital AVF. For clinicians, the temptation is to create a BCF as this tends to mature and function as a working fistula; avoiding multiple attempts at establishing a suitable fistula for haemodialysis. There is also a concern of “surgical / patient fatigue” following multiple attempts at fistula creation causing disillusionment and disengagement, which might result in patients refusing further operations and instead favouring long-term tunnelled catheters for dialysis. Indeed, current data suggests that patients are likely to remain with the first successful dialysis modality [122,123], therefore establishing a functional AVF in the first instance is critical.

Creation of an arteriovenous fistula involves anastomosing a high pressure, high flow artery to a low resistance, low flow vein. The net result is the creation of a high flow, low resistance non-anatomic circuit [72,124,125]. There is reduced flow in the artery distal to the anastomosis, and consequently to the distal extremity. This phenomenon of limb

hypoperfusion distal to the access site is termed “steal”. In healthy vessels, there is dilatation of the proximal and distal arteries, compensating for enhanced systolic AV flow and for diastolic retrograde inflow into the fistula. Vessel remodelling takes place over the course of several weeks. This increase in blood flow is dramatic and is critical to fistula maturation [41].The individual compensates with an increase in heart rate and thus cardiac output. Any vascular pathology affecting these adaptive mechanisms can cause distal ischaemia by a steal mechanism. If a stenosis is present within the artery proximal to the anastomosis, less blood is delivered distally. Blood still preferentially flows into the low resistance fistula, leaving a reduced flow to be delivered distally. If the distal vessels are arteriosclerotic, this results in increased distal resistance, and blood preferentially travels down the low resistance path. Steal syndrome may occur immediately or evolve over several weeks and is often intensified during dialysis. Between 50-66% of patents who develop steal do so within one month of surgery [71,126].

As described in Chapter 1, steal is a clinical phenomenon which manifests itself in 4 stages (Table 1.2). Asymptomatic steal (Grade 0), demonstrated by a weakened pulse, reduced Doppler signals and diastolic distal flow reversal on duplex ultrasound, may be present in the access but only become symptomatic when blood flow is shunted from tissue beds distal to the arterial anastomosis. The incidence of mild and moderate steal is unknown. Mild ischaemia (Grade I) may be self-limiting and may resolve with conservative management. Severe ischaemic symptoms of steal can be long-lasting and may be associated with constant pain, numbness, distal cyanosis or gangrene (Figure 3.2). Whilst symptomatic steal can occur with distal (radiocephalic) AV access, incidence is low, ranging from 0.25-1.8% [75,114,127]. Severe ischaemia is most frequently associated with a brachial artery inflow (BCF/BBF), with frequency ranging from 4-9% [75,110,114]. Overall, the incidence of severe steal is 0.5-5% within the haemodialysis population [71,128]. Other factors associated with the development of ischaemic steal include diabetes mellitus, previous ipsilateral AV access, female gender and age.

Figure 3.1: Digital gangrene of left middle finger in a haemodialysis patient

3.2 Rationale of the study

The manifestation of steal is a result of inadequate blood flow to the distal extremity. Utilising the proximal radial or ulnar artery instead of the brachial artery as arterial inflow (Figure 3.2) might be a solution to reduce the incidence of steal, which would provide an adequate arterial inflow to allow fistula maturation and subsequent haemodialysis while offering a potential option for surgical revision if the fistula eventually fails. Distal hand perfusion can be maintained by the concomitant arterial circulation via the palmar arch. There have been no randomised studies to date examining the rates of steal syndrome and steal phenomena in fistulae utilising brachial arterial inflow versus fistulae utilising proximal radial/proximal ulnar arterial inflow. Given the lack of supporting data, a state of clinical equipoise exists; there is genuine uncertainty as to which intervention is superior.

3.3 Trial design

This study is a randomised controlled clinical trial which is single blinded, intention-to-treat and active control. The duration of candidate participation was 6 months. Figure 3.3 details the referral pathway. Participants underwent one pre-trial consultation and informed consent meeting, one pre-intervention assessment and randomisation session, the intervention, one post-intervention telephone interview and three post-intervention assessments. This study procedure is further described in Section 3.8 and summarised in Figure 3.4.

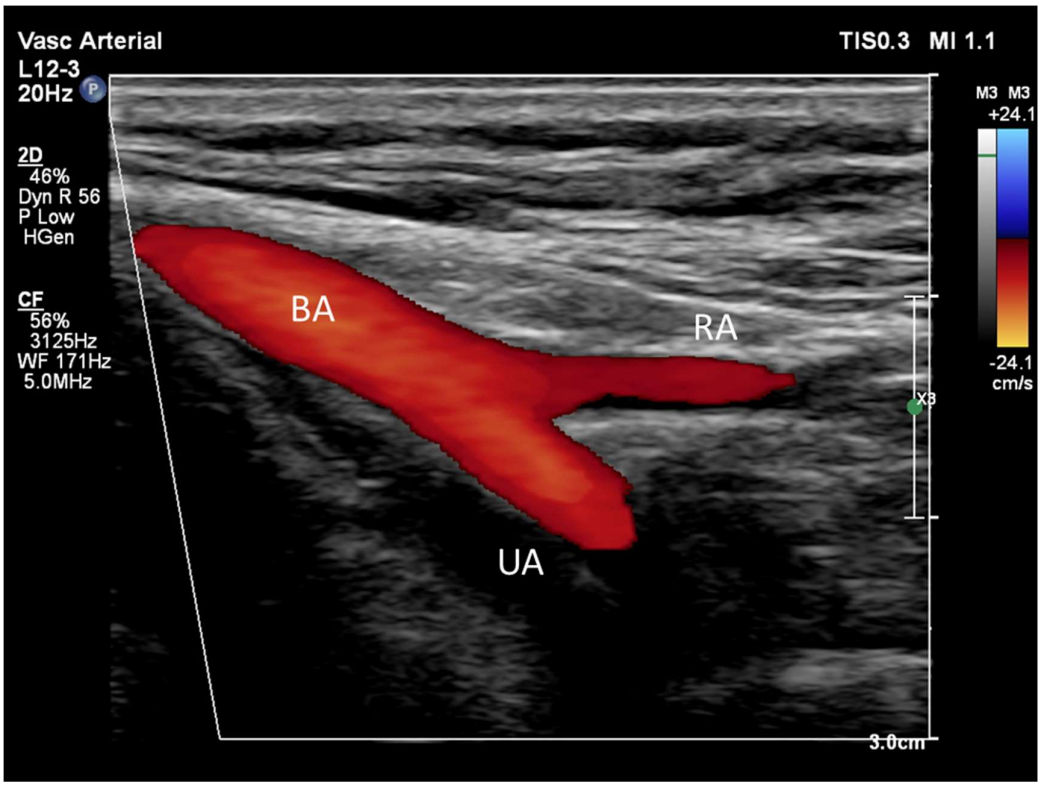


Figure 3.2: Ultrasound image depicting brachial artery (BA) bifurcating into radial (RA) and ulnar (UA) arteries

3.4 Objectives and endpoints

3.4.1 Primary objective

This study aims to determine if patients with a fistula utilising the proximal radial/ulnar artery as arterial inflow have a lower incidence of steal symptoms compared to patients with a fistula employing the brachial artery as inflow at up to 6 months following fistula creation. Grading of steal symptoms would be as per Table 1.2.

3.4.2 Primary endpoint

The primary endpoint is the incidence of steal syndrome as measured by the Steal symptom score at 6 months following fistula creation. The Steal symptom score and its derivation has previously been detailed in Section 2.3.6.

3.4.3 Secondary objectives

The secondary objectives are:

- To ascertain if there is a change in DP or DBPI before and after AFF creation and how this correlates to steal symptoms
- The fistula survival rate of the two types of AFF for haemodialysis
- The efficacy of the two study interventions in terms of complication rate
- To incidence of severe steal requiring surgical intervention (revision/ligation) between the 2 study interventions

3.4.4 Secondary endpoints

The secondary outcomes are:

- Grade of ischaemic steal syndrome
- DP and DBPI at 3 weeks, 3 months and 6 months
- Primary patency at 6 months
- Complication rate, including surgical revision

3.5 Ethics

3.5.1 Ethical approval

This study was conducted in full conformity with the Declaration of Helsinki [129] and adhered to the standards of the International Conference on Harmonisation Good Clinical Practice. The protocol, informed consent form, participant information sheet was submitted to the Cambridgeshire 2 Research Ethics Committee, Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge, for written approval.

Ethical approval was granted by the Cambridgeshire 2 Research Ethics Committee, REC reference number 10/H0308/90 (refer to appendix). This study was registered with ClinicalTrials.gov, ID number NCT02297451.

3.5.2 Confidentiality

Trial staff ensured that participants' anonymity was maintained. This was achieved by only using a study specific participant ID number to identify the participant on the trial documentation and any electronic database. All documents were stored securely and only accessible by trial staff and authorised personnel. The study complied with the Data Protection Act and data was anonymised as soon as it was practical to do so.

3.5.3 Other Ethical Considerations

The trial did not include any vulnerable individuals or the minors; all trial participants were required to be able to consent freely. There was no placebo or true control group. All participants received one of the two trial interventions. Intervention A (BA-AFF) acts as the active control group. Intervention B (PRA/PUA-AFF) requires longer operative time and a more extensive dissection for arterial access and therefore may carry an increased risk of technical complications. There is insufficient data in existing studies to support this. We propose that the potential benefit of having a lower risk of steal syndrome will outweigh this risk.

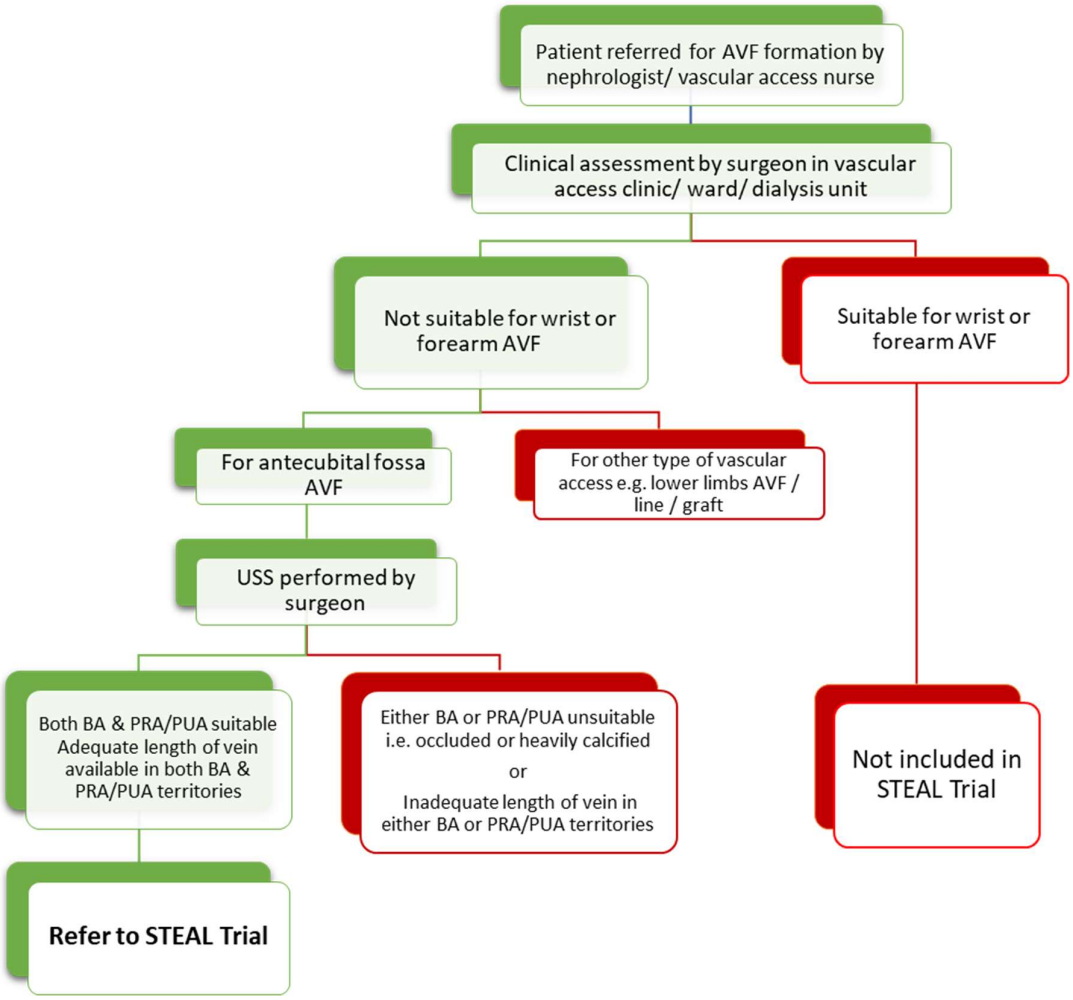


Figure 3.3: Referral Pathway

3.6 Study centre

The study was conducted in Addenbrookes Hospital, Cambridgeshire, UK. This university teaching hospital provides a tertiary referral vascular access service as well as renal transplants for East Anglia. Addenbrookes Hospital together with satellite units located in King's Lynn, Bury St Edmunds and Hinchingbrooke Hospitals serve a haemodialysis population of approximately 400 patients. We perform approximately 200 vascular access procedures annually. The necessary presence of clinical expertise and equipment required for this study is well established in our unit.

3.7 Trial participants

3.7.1 Inclusion criteria

The study was inclusive. All patients aged ≥16 years diagnosed with end stage renal failure necessitating long-term haemodialysis were eligible to participate. Firstly, they had to be willing and able to provide informed consent for participation in the trial. Patients had to require an AVF in the antecubital fossa for vascular access. In terms of anatomy, both brachial and proximal radial (or ulnar) arteries had to be suitable (not severely arteriosclerotic, not stenotic, no high bifurcation, calibre >2mm) as arterial inflow in AVF creation when assessed via ultrasound; the patient must in theory be able to undergo either intervention. Similarly, the venous component of the fistula must be of suitable calibre (>2mm) and have sufficient length for AVF creation regardless of the type of fistula randomised; creation of a proximal radial (or ulnar) fistula must not necessitate transposition of a more distal vein which would require significantly more extensive dissection.

3.7.2 Exclusion criteria

Patients were excluded if a more distal fistula could be fashioned in the first instance (i.e., RCF or ulnarbasilic fistula [UBF]). Patients were also excluded from the study if on ultrasound assessment the brachial or the proximal radial / ulnar arteries were not suitable for fistula formation (for example, occluded with no flow on colour doppler or heavily calcified), or if there was insufficient length of vein extending to the territory of the proximal radial and ulnar arteries, making fistula formation technically unfeasible.

3.8 Study procedure

3.8.1 Outline

Each participant underwent a pre-trial consultation and informed consent meeting, a pre-intervention assessment and randomisation session, the intervention, one post-intervention telephone interview and three post-intervention assessments. This process is detailed in Figure 3.4.

3.8.2 Referral to STEAL trial and consultation

Potential participants were referred to the investigator by the vascular access surgeon once the decision was made to create an antecubital fossa fistula. Typically, patients would present following vascular assessment in the vascular access clinic, on the ward or via the dialysis unit. These potential participants were approached and given verbal and written information about the trial detailing the aims of the study, the procedure, and potential risks and benefits (Appendix 7.3 Participant Information Sheet). The contact details of the investigator was provided so that questions could be raised and concerns addressed before a decision was made as to whether to participate.

3.8.3 Informed consent

Following identification of suitable candidates, written and verbal information was provided to the patients during the first interview which detailed the nature of the study, any known potential risks involved and the study protocol. It was also made explicit that should the candidate choose not to participate in the study, that this would not prejudice them against any further treatment. The candidate was allowed to consider the information provided and ask any questions before deciding whether to participate in the study.

Written consent was obtained at a later date once the participant has had an opportunity to raise any concerns. The participant signed a written consent form and a copy was given to the patient. The consent form was retained and filed in a secure area at the study site.

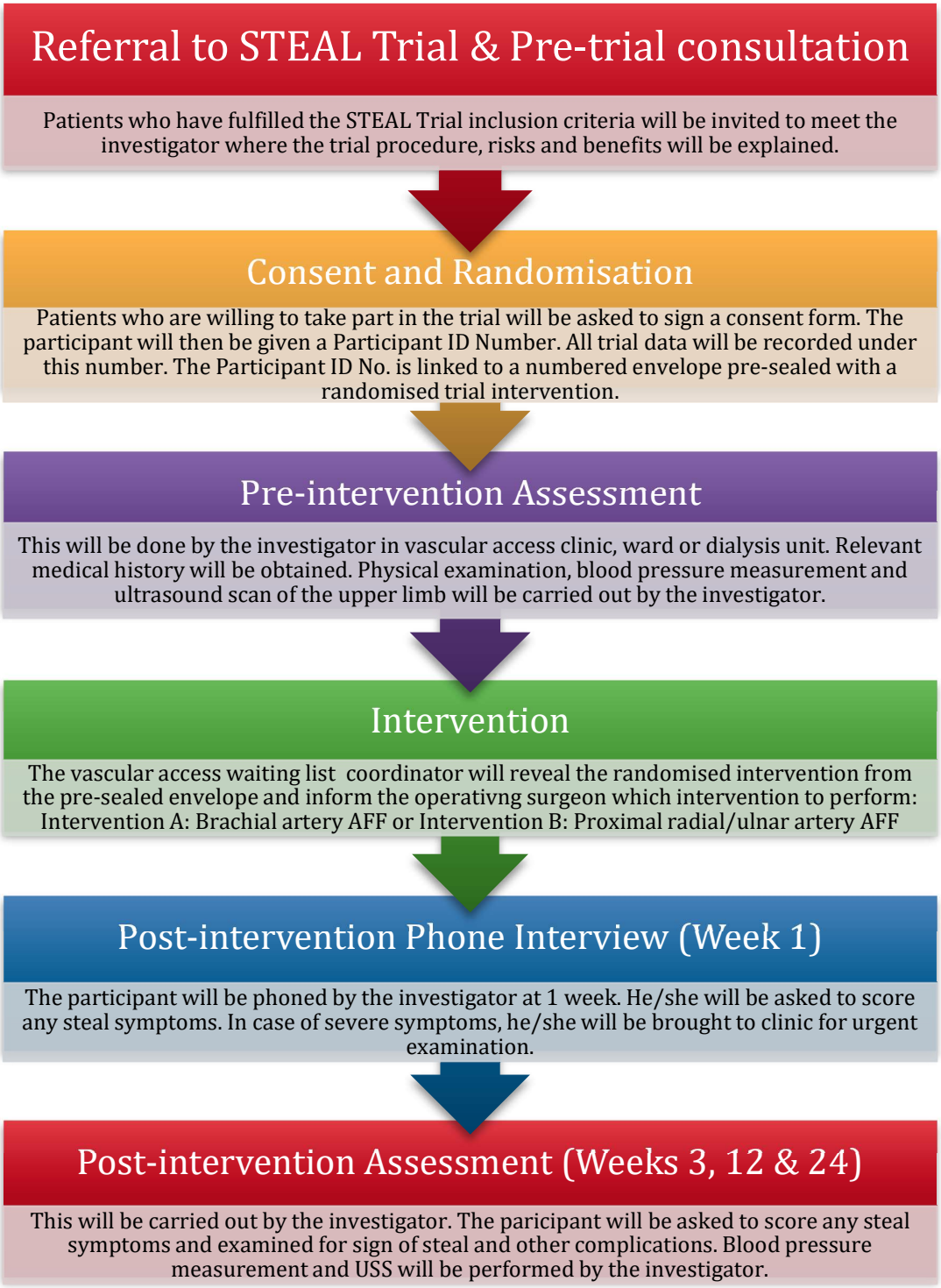


Figure 3.4: STEAL trial pathway

3.8.4 Pre-intervention assessment and recruitment

During the pre-intervention assessment, the demographic data, medical history and medications of the participants were recorded. Vascular assessment was then carried out to act as a baseline assessment and to determine the eligibility of the participant. Brachial blood pressure was measured using a conventional blood pressure machine. Measurements were also recorded from the contralateral arm. Digital blood pressure was measured using the Huntleigh DopplexAssist^{TM} (Huntleigh Healthcare Ltd, Wales, UK). An inflatable cuff is placed around the proximal phalynx of the index finger, with the sensor placed on the distal phalynx. The digital brachial pressure index (DBPI) is then calculated as the ratio of finger pressure to systolic blood pressure.

An ultrasound assessment using the Sonosite MicroMaxx® (Fujifilm SonoSite Inc, Washington, USA, Figure 3.5) was used to assess the patency (patent/stenotic), size (>2mm) and quality (degree of arteriosclerosis) of the vessels in question. The key determining factor for eligibility to take part in the study stems from the assessment of the length of the cephalic or basilic vein. There must be sufficient length of vein to potentially transpose the vein to either the proximal radial or ulnar arteries. Should the vein be deemed not to have adequate length, then that person was deemed ineligible for study inclusion. Arterial duplex was not performed as this is not a routine investigation performed prior to AVF formation. Following inclusion, a participant ID was then allocated, which is linked to a randomisation number, representing the randomised intervention.

Figure 3.5: SonoSite MicroMaxx® Ultrasound System

3.8.5 Randomisation

Permuted block randomisation is used with an allocation ratio of 1:1. The randomisation sequence was generated at the start of the trial prior to patient recruitment by a neutral third party, in this case Dr Richard Parker, statistician at the Centre for Applied Medical Statistics from the University of Cambridge. An independent trial coordinator was responsible for transcribing the randomisation sequence into individual interventions and these were then sealed sequentially in opaque envelopes numbered according to the randomisation sequence. Each envelope is linked to a participant ID, and the envelope was opened prior to the operation. Due to the nature of the intervention, the participant was blinded to the intervention received, but the surgeon was not.

3.8.6 Intervention

An arteriovenous fistula consists of 2 components: the arterial inflow and the venous outflow. This study aims to characterise the effect of the 2 different types of arterial inflow on steal syndrome.

Participants receive one of the following study interventions:

Intervention A (control): Fistula creation utilising the brachial artery as inflow

Intervention B: Fistula creation using either the proximal radial artery or proximal ulnar artery as inflow

All possible venous outflow types are included in this study. The venous outflow utilised will be decided by the assessing or operating surgeon at the initial vascular assessment depending on the patency, size of vein and its course across the antecubital fossa.

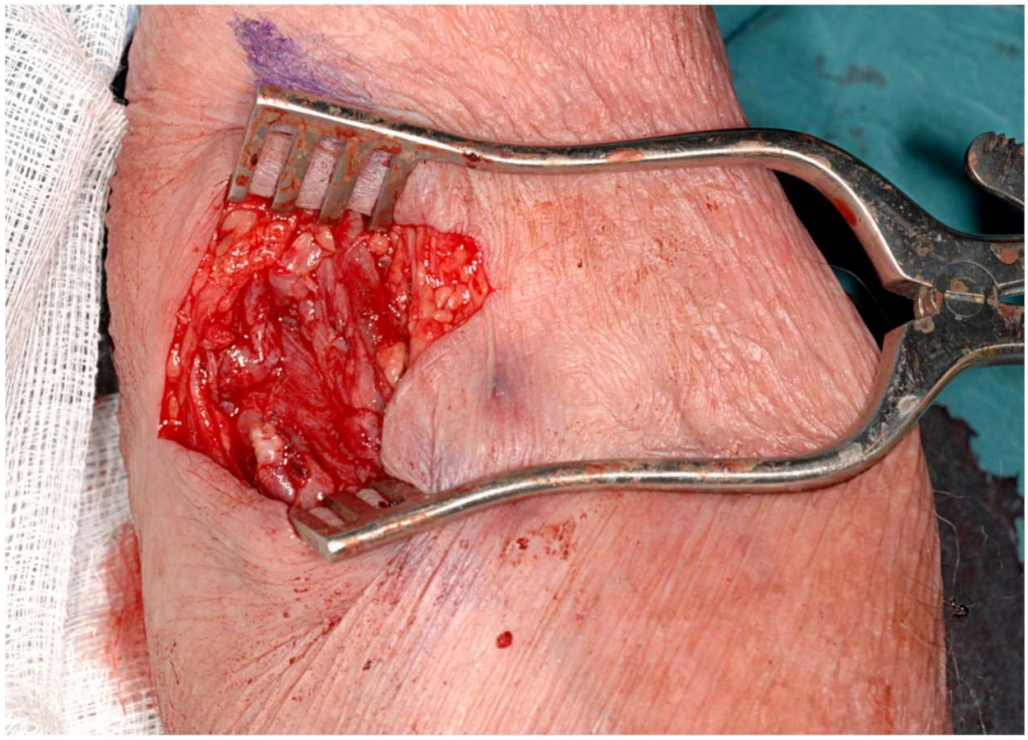
The types of venous outflow include:

1. Cephalic vein
2. Median cubital vein
3. Basilic vein – when this is used, the basilic vein is transposed and superficialised. This requires more extensive dissection. In our unit this was typically performed as a single stage procedure under general anaesthesia, as opposed to a two-stage procedure favoured by some units.

The surgical procedure was performed by a total of 2 experienced consultant transplant surgeons and a team of senior trainees under consultant supervision. The surgeons generally followed a standard operating technique, using ultrasound to mark vessel position preoperatively and plan the appropriate incision (Figure 3.6). Almost all fistulae were created under local anaesthetic, with the exception of brachiobasilic fistulae. The vein was flushed with heparinised saline to ensure good distension. Operating loupes with x2.5 magnification and micro-instruments were used to form an end-to-side anastomosis. At the end of the operation, the operating surgeon completes a trial specific record of the

intervention performed. A copy of the form is included in the appendix {Section 7.5 Trial-specific operation record (steal trial)}.

A



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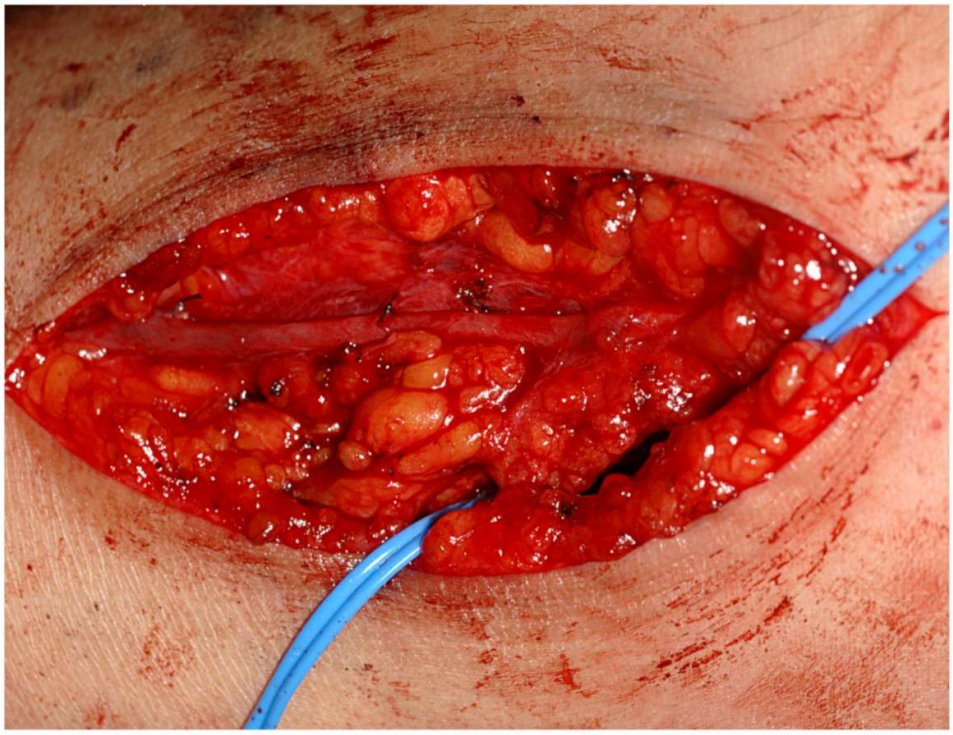

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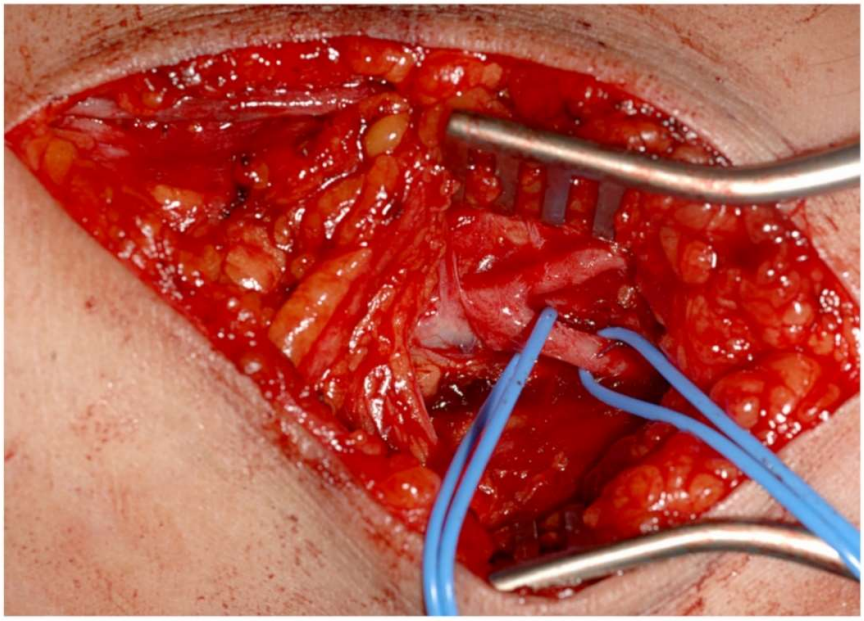

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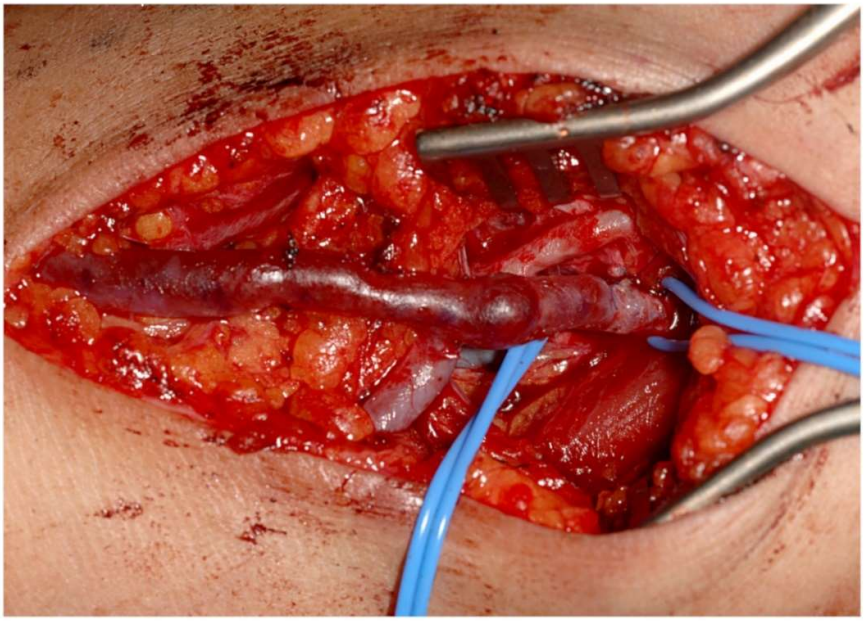


Figure 3.6: Creation of a proximal radial-cephalic fistula

(A) Incision made just distal to the elbow crease at the level of the brachial bifurcation (B) Cephalic vein is mobilised and tributaries tied (C) Brachial artery is identified, radial and ulnar arteries exposed (D) End on side anastomosis created with good distensibility of cephalic vein evident

3.8.7 Follow-up post intervention

After the antecubital fossa fistula is created, patients were evaluated on 4 occasions during a six-month interval (Figure 3.4).

3.8.7.1 Telephone interview at week 1

Participants were contacted and asked a list of questions to screen for symptoms of early steal syndrome or early postoperative complications {Appendix 7.6 Post-intervention assessment form (steal trial)}. If there were any concerns, the patient was brought back to clinic for assessment and, if required, treatment.

3.8.7.2 Clinical assessments

Following intervention, each participant was screened at 3 weeks, 3 months and 6 months.

The following details were recorded:

They were screened for symptoms of steal (cold extremity, pain, paraesthesia, weakness and claudication) and the individual score of each of these five domains are recorded using a visual analogue scale. The Steal symptom score is comprised of the sum total of these five domains. Patients were also examined for signs of steal syndrome (delayed capillary refill time; decreased skin temperature; pallor; decreased sensation and evidence of tissue loss). The grade of ischaemic steal (as outlined in Table 1.2) experienced by the patient was recorded.

The brachial and digital blood pressures were measured. The fistula was examined for patency and any local complications (e.g. infection). The fistula flow rate was determined using duplex ultrasound.

The date of first cannulation was recorded and the date of commencement of regular dialysis (3 consecutive dialysis sessions) was recorded [104].

3.9 Statistical Analysis

This a single centre, single blinded randomised control trial. The active control is the standard treatment (brachial artery fistula [BCF/BBF]). Results are analysed on an "intention to treat" basis unless otherwise stated.

Categorical variables were compared using Fisher's exact test. Kaplan-Meier survival analyses and Log-rank tests were used to analyse fistula survival. In keeping with reporting standards recommended by the North American Vascular Access Consortium [36], fistulae that failed within 72 hours were deemed to have failed at time zero. Patients were censored in the event of death or final measurement of patency. All analyses were performed with GraphPad Prism (v.5.03 GraphPad Software Inc, CA, USA).

3.9.1 Sample size calculation

From a previously unpublished pilot study performed at our institution, we calculated that 43 patients are required in each intervention group to provide 80% power to detect a 25% difference in the incidence of Steal syndrome at 6-month follow up with an $\alpha = 0.05$. To account for attrition / loss to follow up of 15%, we aim to recruit 100 patients (50 in each arm).

3.10 Interim Results

From April 2011 - January 2017, all patients referred for creation of an antecubital fistula were assessed for eligibility. A total of 68 patients were recruited. The trial profile is detailed in Figure 3.7. Two patients were excluded; one withdrew from the study/dialysis and the other patient had a radiocephalic fistula created on table instead. A total of 66 patients were randomly assigned to an intervention. Demographic data is detailed in Table 3.1; both groups were well matched. Thirty-four patients were randomised to Intervention A and thirty-two were randomised to Intervention B. Sixty-five patients completed 6-month follow up. One patient was lost to 6-month follow up.

3.10.1 Steal symptom score at 6 months

At 6 months, there was no significant difference in the scores of both groups (Figure 3.8, P = 0.585, Mann-Whitney U test, intention to treat analysis). There was no significance difference in subgroup scores between both interventions (Figure 3.9). When the analysis considered the actual intervention performed, this did not reveal any significant difference between both interventions.

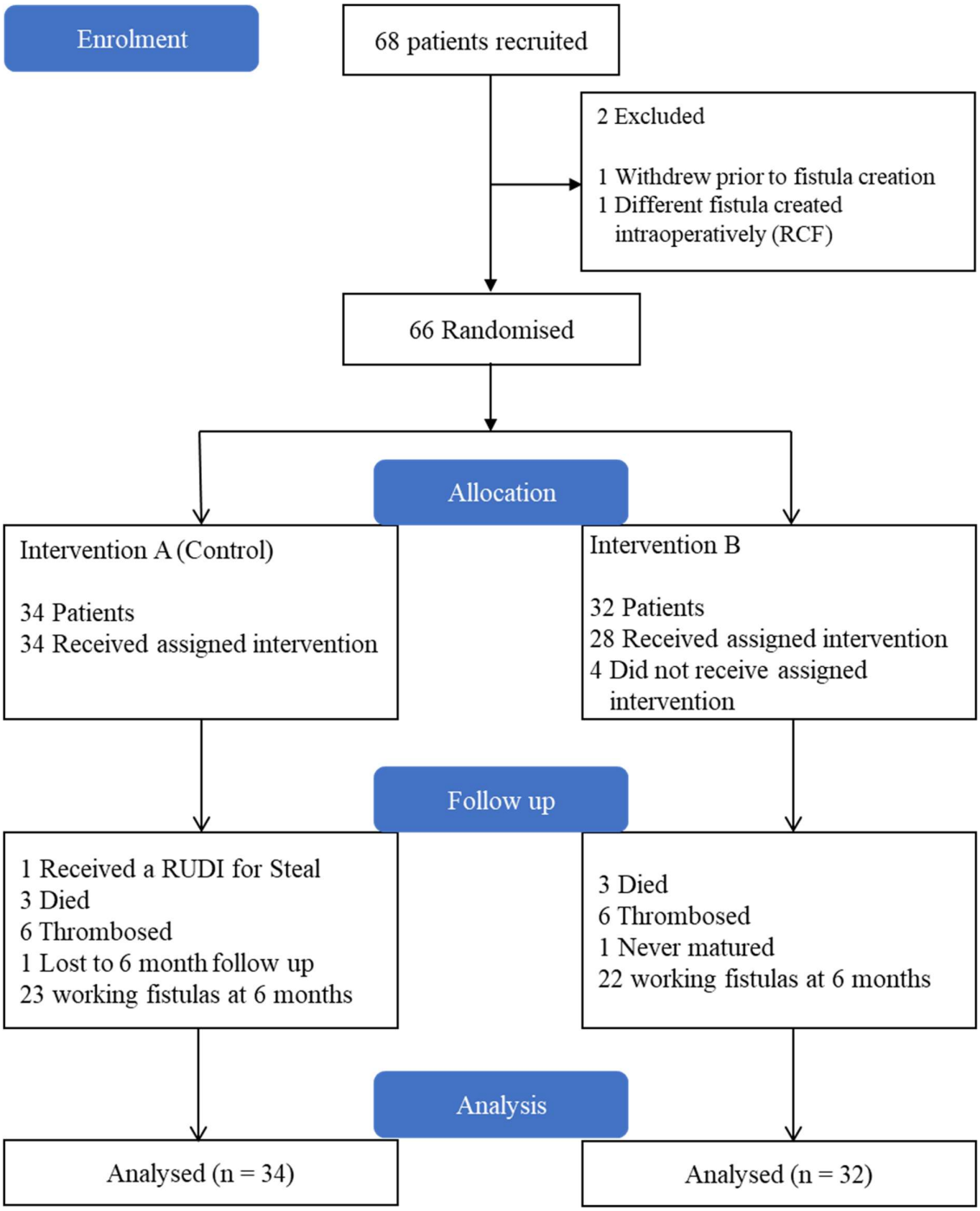


Figure 3.7: Trial Profile

	Entire Cohort (N = 66)	Intervention A (N = 34)	Intervention B (N = 32)	P value[a]
Age years mean (SD)	69 (11.3)	67 (12.8)	71 (9.4)	0.183[b]
Gender m:f	32:34	19:15	13:19	0.215
Comorbidities				
Ischaemic heart disease	19 (30.6)	11 (32.4)	8 (25.0)	0.592
Hypertension	29 (43.9)	15 (44.1)	14 (43.8)	0.976
Diabetes				
Total (%)	21 (31.8)	13 (38.2)	9 (28.1)	0.384
Type I	3 (4.5)	2 (5.9)	1 (3.1)	
Type II	19 (28.8)	11 (32.4)	8 (25.0)	
Smoking history				0.644
Smoker (%)	11 (16.7)	6 (17.6)	5 (15.6)	
Ex-smoker (%)	6 (9.1)	2 (5.9)	4 (12.5)	
Non-smoker (%)	49 (74.2)	26 (76.5)	23 (71.9)	
Peripheral vascular disease (%)	5 (7.6)	4 (11.8)	1 (3.1)	0.357[c]
Aetiology of Chronic Kidney Disease				
Diabetic nephropathy (%)	10 (15.2)	7 (20.6)	3 (9.4)	0.306[c]
Urological disease (%)	8 (12.1)	2 (5.9)	6 (18.8)	0.143[c]
Glomerulonephritis (%)	5 (7.6)	3 (8.8)	2 (6.3)	1.000[c]
Hypertensive nephropathy (%)	5 (7.6)	3 (8.8)	2 (6.3)	1.000[c]
Adult polycystic kidney disease (%)	4 (6.1)	2 (5.9)	2 (6.3)	1.000[c]
Idiopathic (%)	21 (31.8)	13 (38.2)	8 (25.0)	0.297
Other (%)	13 (19.7)	9 (26.5)	4 (12.5)	0.154

Table 3.1: Demographics and comorbidities

[a] All p values were calculated via $\chi 2$ test unless otherwise stated, comparison made between Intervention A and B; [b] unpaired t-test; [c] Fischer's exact test

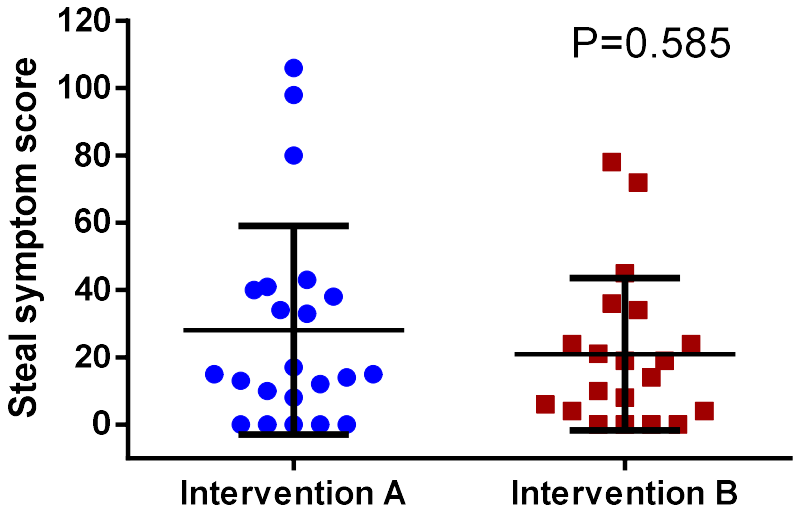


Figure 3.8: Steal symptom score distribution at 6 months (Intention to treat analysis)

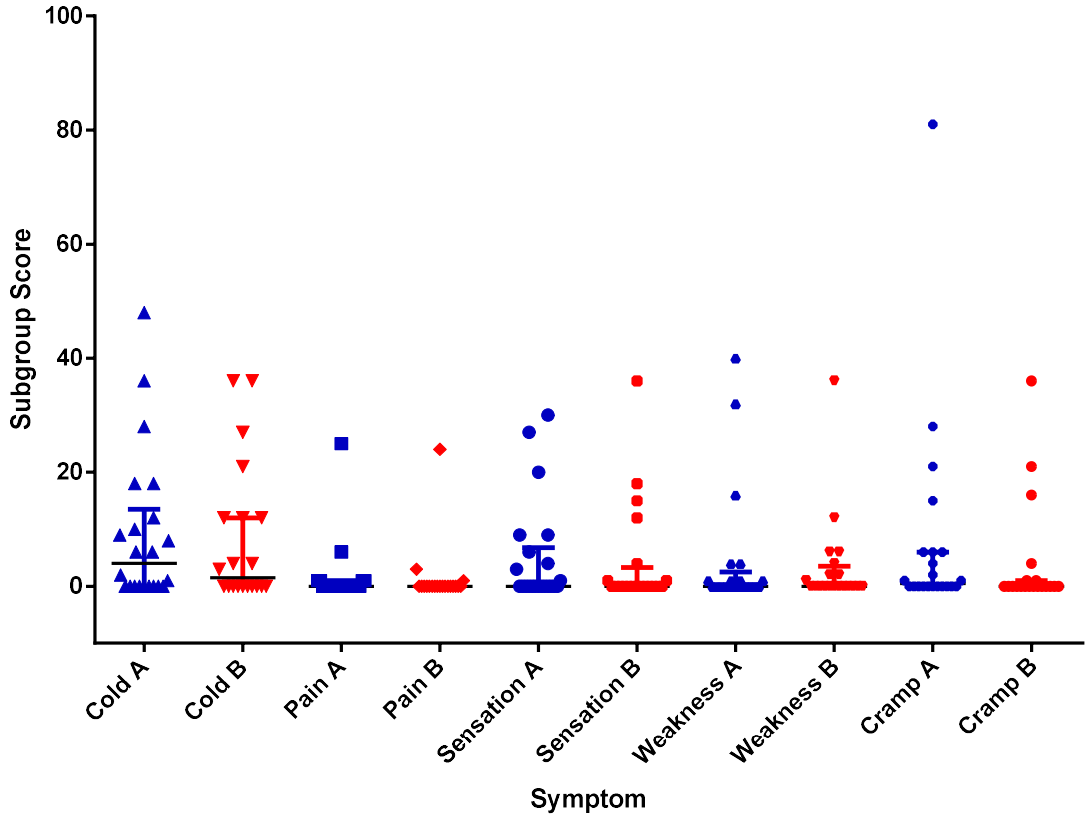


Figure 3.9: Subgroup breakdown

3.10.2 Distribution of steal symptoms in the cohort

The distribution of grade of steal according to intervention randomised is detailed in Figure 3.10. The maximal symptom score during the 6-month study interval was used. Twenty-four patients in the cohort were asymptomatic (9 received intervention A and 15 received intervention B). A further nineteen displayed mild symptoms of steal (Grade 1). When comparing asymptomatic (Grade 0) to symptomatic patients (incorporating mild and severe symptoms [Grades 1-4]) in both interventions, there was a significant difference (P = 0.0381, Fischer's exact test). The $\chi 2$ test could not be used in this instance to analyse for each individual category (0-4) as $\chi 2$ calculations are only valid when all expected values are greater than 1 and at least 20% of the expected values are greater than 5. Therefore, they were grouped as such. The difference between both interventions is more striking when we consider largely asymptomatic patients (Grades 0-1) versus patients with more severe and debilitating symptoms (Grades 2-4). This second analysis was performed because, as clinicians we would be more concerned with patients presenting with moderate to severe symptoms (Grades 2-4), and further deterioration might require intervention. There is a significant difference between both interventions (P = 0.0024, Fischer's exact test).

Whilst Intervention B still results in a degree of ischaemia resulting in cold hands, it appears that the more debilitating symptoms of steal are less likely to manifest. When considering the actual intervention performed rather than an "intention-to-treat" analysis, the results remain significant (P = 0.0332 and P = 0.0059 respectively, Fischer's exact test).

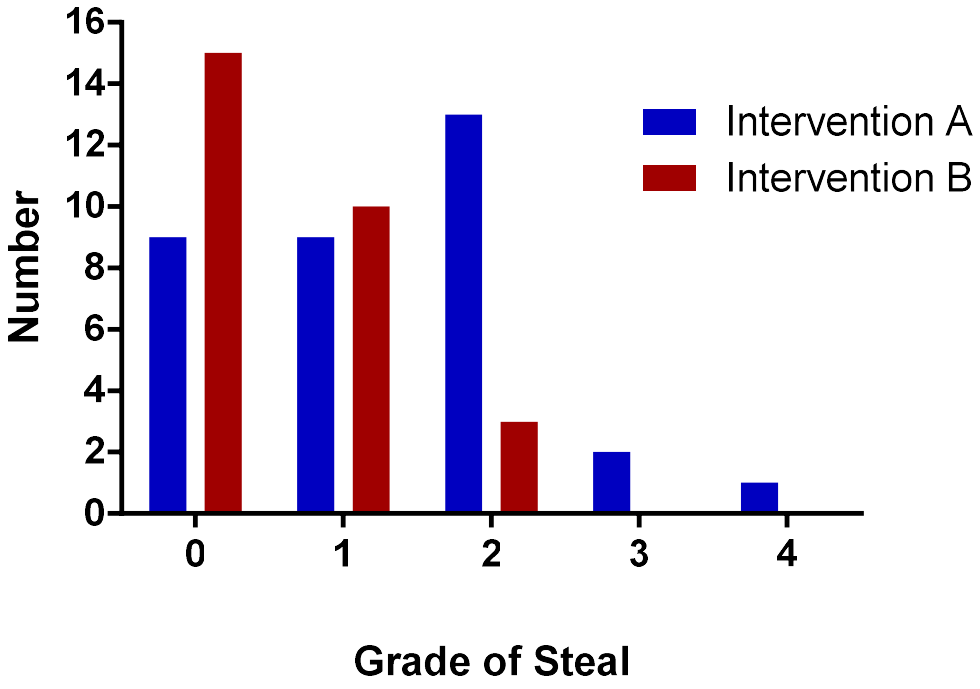


Figure 3.10: Distribution of grade of steal by type of intervention (Intention to treat analysis)

3.10.3 DP, DBPI and grade of steal

Pre-operatively, there was no significant difference in the DP and DBPI of both interventions (Figure 3.11 and Figure 3.12, P = 0.259 and P = 0.124 respectively, Mann-Whitney U test). When comparing the pre-intervention DP to the DP at 3 weeks, there was a significant difference (P = 0.001 and P = 0.0006, Intervention A and Intervention B respectively, Wilcoxon matched-pairs signed rank test). The median reduction in DP following operation was 23mmHg in Intervention A and 29mmHg in Intervention B, but this was not statistically significant (P = 0.652, Mann-Whitney U test). Similarly, there was a reduction in DPBI postoperatively, with the mean DBPI reduction in Intervention A of 0.18 and in intervention B of 0.25, this reduction however was not significant (P = 0.401, unpaired t-test).

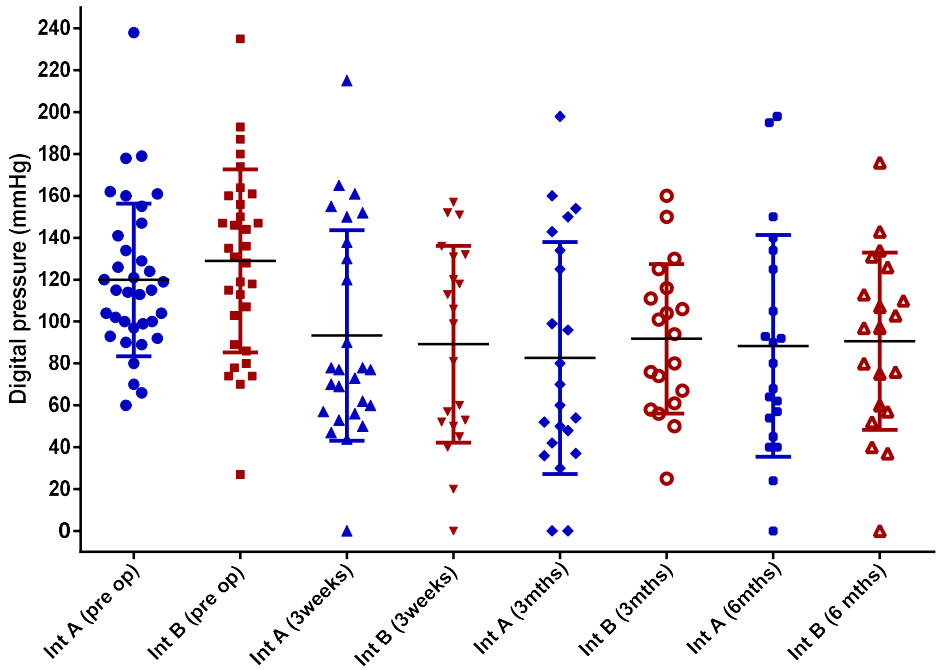


Figure 3.11: Distribution of DP for both interventions at various time points

Error bars denote standard deviation and black line denotes mean

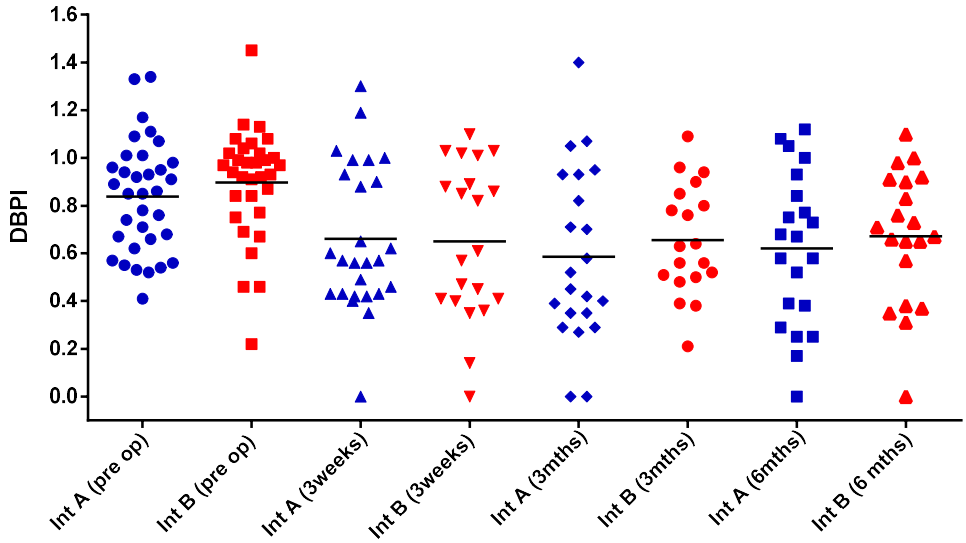


Figure 3.12: Distribution of DBPI for both interventions at various time points

Black line denotes mean

When the pre-operative DP of the cohort was graphed against the eventual grade of steal experienced (Figure 3.13), there was a clear trend in lower pre-operative DP giving rise to more severe grades of steal. This trend was also similar when considering the preoperative DBPI (Figure 3.14). There was a solitary individual who had experienced grade 4 steal, necessitating surgical intervention.

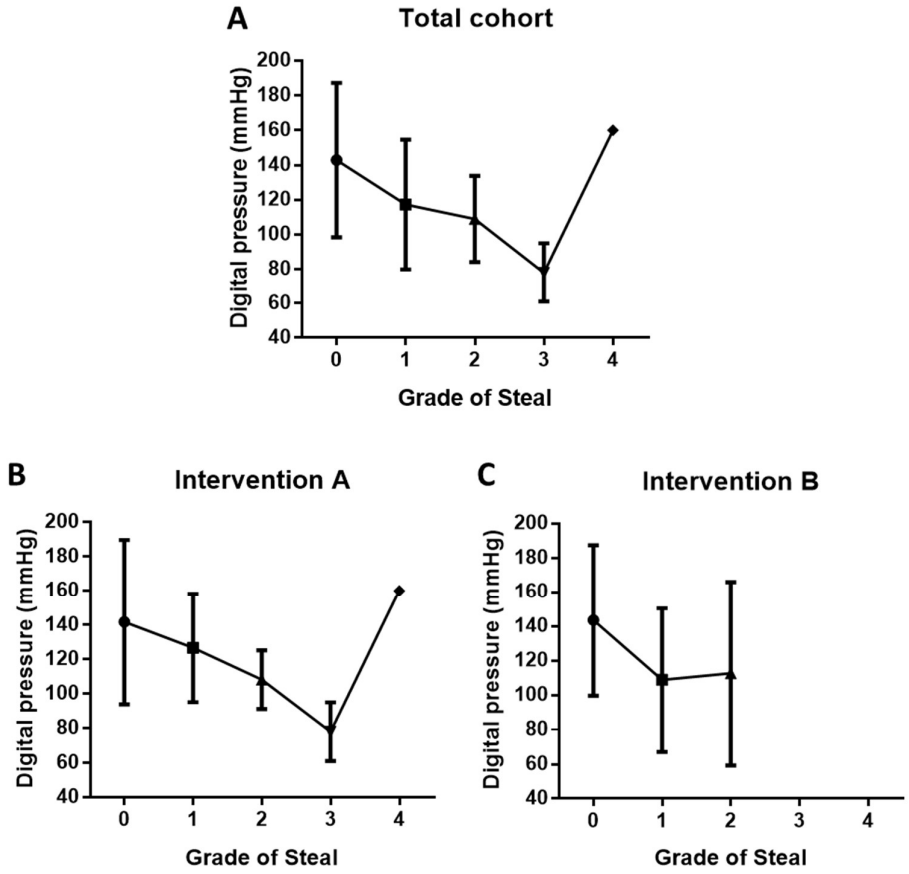


Figure 3.13: Pre-intervention DP and associated grade of steal

(A) Total cohort (B) Intervention A (C)Intervention B

The centre dot represents the mean and the error bars denote the standard deviation. Note that in graphs A and B, there was a single individual who experienced grade 4 steal. In graph C, no individuals experienced grade 3 or grade 4 steal.

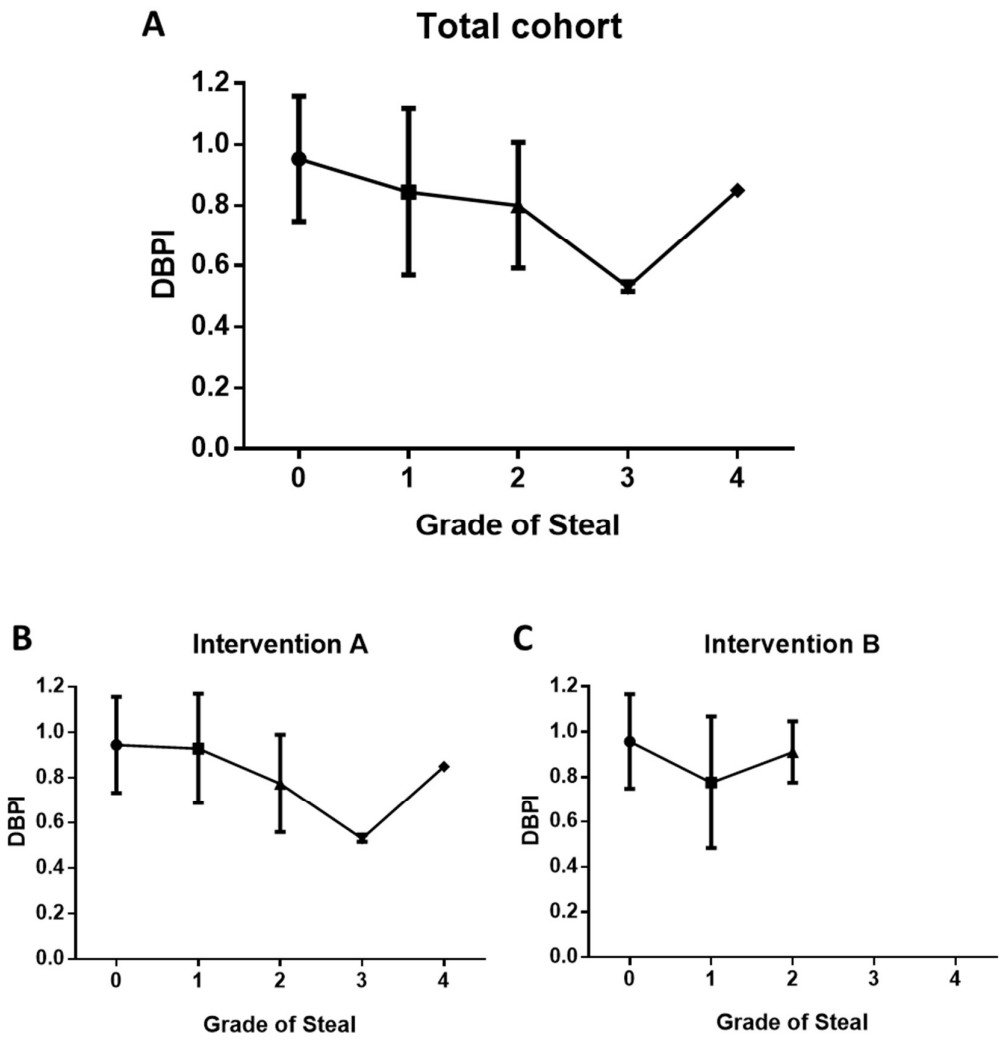


Figure 3.14: Pre-intervention DBPI and associated grade of steal

(B) Total cohort (B) Intervention A (C)Intervention B

The centre dot represents the mean and the error bars denote the standard deviation. Note that in graphs A and B, there was a single individual who experienced grade 4 steal. In graph C, no individuals experienced grade 3 or grade 4 steal.

Comparing the post-operative DBPI of all patients to the grade of steal experienced, there is a clear trend of decreasing DBPI as severity of steal increases (Figure 3.15). When comparing the post-operative DBPIs of largely asymptomatic patients (Grades 0-1) versus patients with more severe and debilitating symptoms (Grades 2-4), there is a significant difference of the DBPI between both groups ($P < 0.0001$, unpaired t-test).

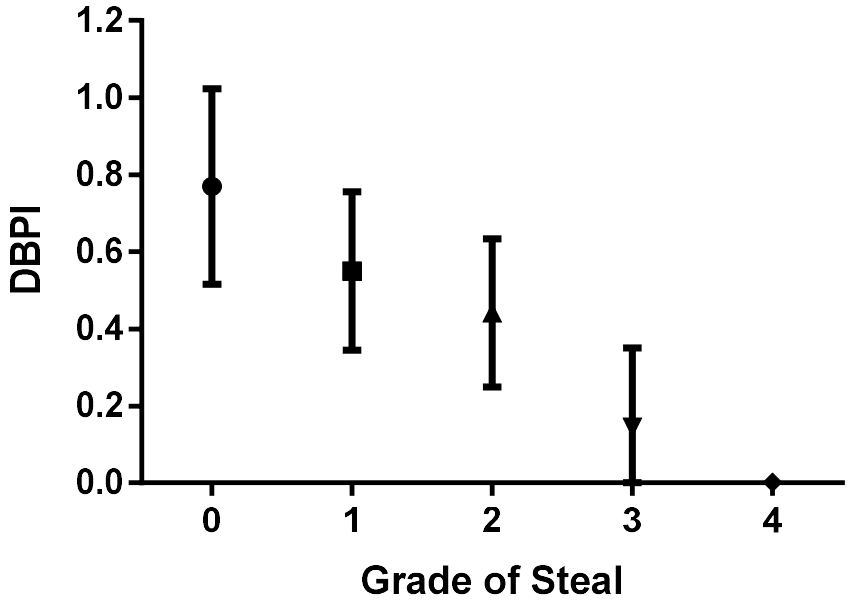


Figure 3.15: Post intervention DBPI and associated grade of steal of all patients

The centre dot represents the mean and the error bars denote the standard deviation.

Finally, when the cohort was stratified according to eventual grade of steal experienced (Figure 3.16), it can be seen that individuals who experience more severe grades of steal (grades 2-4) generally have a lower DP (mean difference 23mmHg) and DBPI (mean difference 0.13) preoperatively when compared to those who were asymptomatic or had mild symptoms, and this was statistically significant (P = 0.034 and P = 0.041 respectively, unpaired t-test).

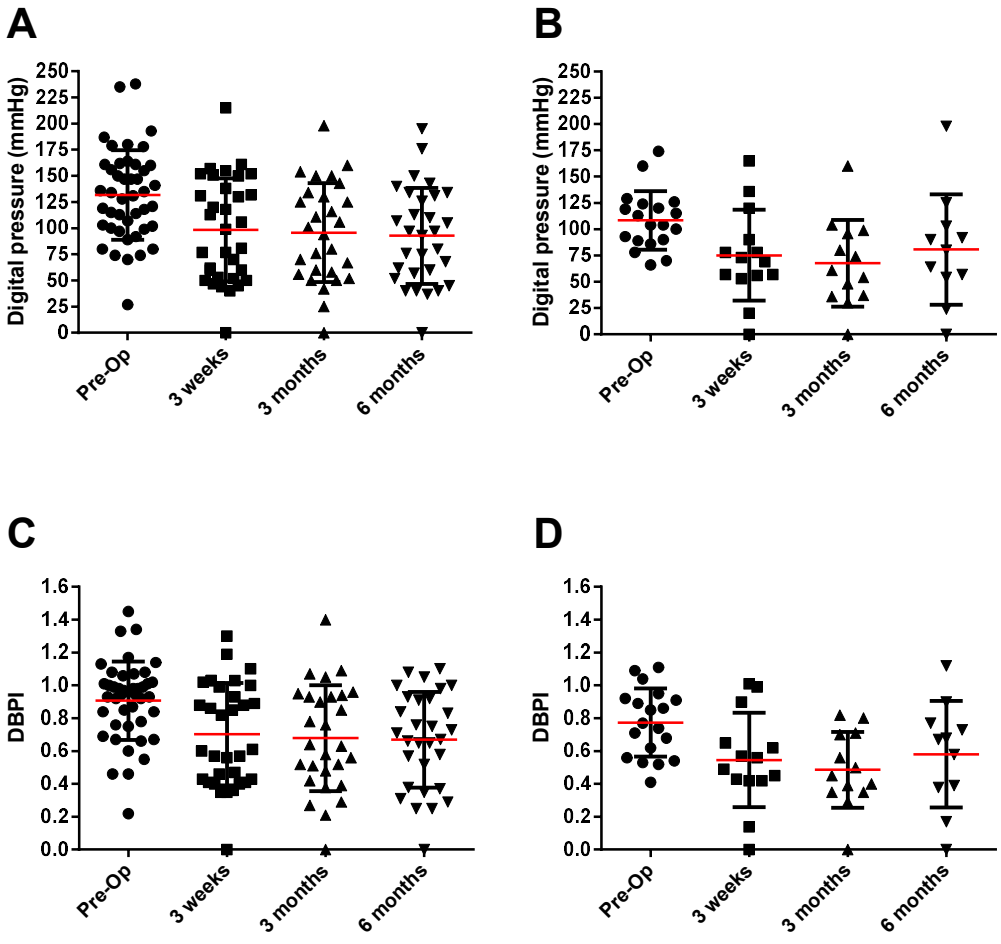


Figure 3.16: Cohort distribution of DP and DBPI according to grade of steal

(A) DP – Steal grade 0-1 (B) DP – Steal grade 2-4 (C) DBPI – Steal grade 0-1

(D) DBPI – Steal grade 2-4

3.10.4 Fistula survival

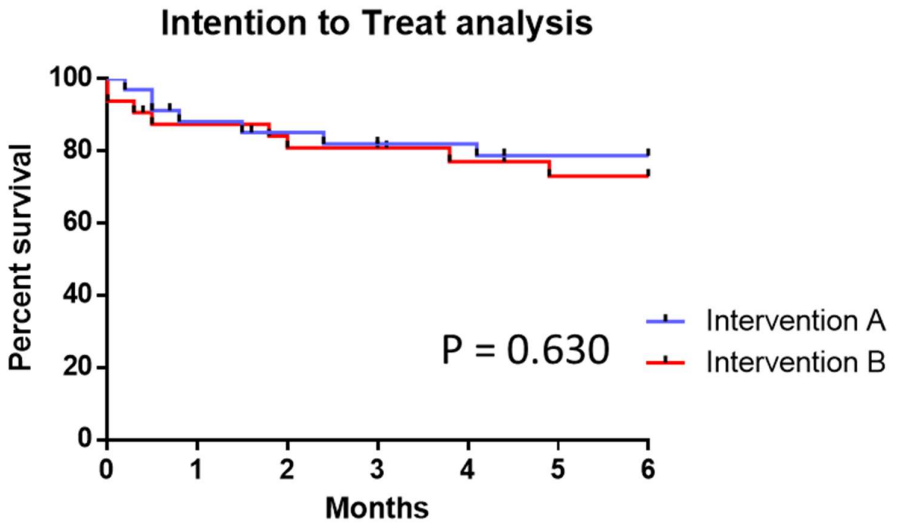
Six months outcomes are detailed in Table 3.2 – for Intervention A, 23 fistulae remained functional and in use; For Intervention B, 22 fistulae remained patent. There was no significant difference in six-month outcomes between both interventions (Table 3.2, χ^2 test, P = 0.964).

When considering fistula survival over 6 months, there was no significant difference in fistula survival between both interventions (P = 0.630, Log-rank test, intention to treat analysis, Figure 3.17). This also held true when considering the actual intervention performed (P = 0.633, Log-rank test, Figure 3.17).

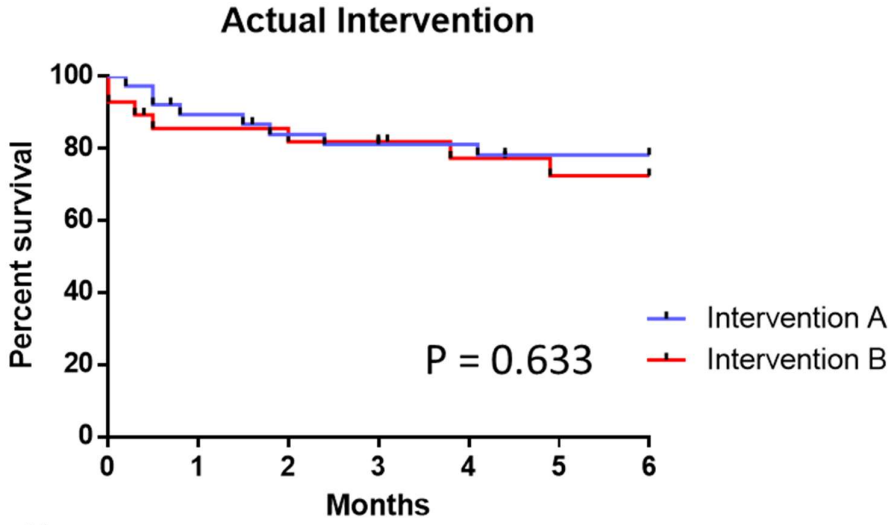
	Intervention A (n = 34)	Intervention B (n = 32)	χ^2 test
Functional	23 (67.6%)	22 (68.8%)	P = 0.964[a]
Thrombosed	6 (17.6%)	6 (18.8%)	
Failed to mature	0	1 (3.1%)	
Not used (unrecognised central venous stenosis)	1 (2.9%)	0	
Patient death / withdrawn from haemodialysis	3 (8.8%)	3 (9.3%)	
Intervention for Steal	1 (2.9%)	0	

Table 3.2: 6-month outcome of interventions

[a] For the purpose of χ^2 analysis integer values in the categories failed to mature, not used, patient death and intervention for steal were combined for each intervention. This is because χ^2 calculations are only valid when all expected values are greater than 1.



Numbers at risk			
Intervention A	34	26	23
Intervention B	32	25	18



Numbers at risk			
Intervention A	38	29	26
Intervention B	28	22	15

Figure 3.17: 6-month survival (Primary patency) of fistulae according to intervention

Patients who died were censored at time of death.

3.10.5 Complications and patient mortality

One of our concerns while the trial was ongoing was the complication rate with respect to Intervention B; that failure of the fistula might result in patients being unable to receive a further, more proximal fistula on the ipsilateral side. One patient in intervention B had a fistula which failed to mature sufficiently to be utilised for haemodialysis. One patient in Intervention A had a functional fistula which was not utilised due to unrecognised central venous stenosis. A total of six patients died or were withdrawn from haemodialysis (3 patients from each intervention arm) during the study interval (Table 3.2).

Finally, one individual from Intervention A had a revision using distal inflow (RUDI). This patient had a background of diabetic nephropathy causing ESRF, type 2 diabetes, hypertension, previous stroke and peripheral vascular disease. Preoperatively, he had a DBPI of 0.84 and steal symptom score of 0. Clinical examination at that point did not give any indication of digital ischaemia. Over the course of 3 months following formation of a brachiocephalic fistula, he developed severe symptomatic steal, with an unrecordable digital pressure / DBPI, and subsequently underwent a RUDI procedure which resolved his symptoms.

3.11 Limitations

The current results presented are a result of an interim analysis. Only participants were blinded to the type of operation carried out, as the intervention would become apparent to the assessor during ultrasonic assessment of the fistula. This might create ascertainment bias, which is minimised by using a symptom score which is provided by the "blinded" patients prior to the ultrasonic assessment outlined above and by using absolute measurements in other elements during the post-intervention assessment.

Determination of fistula flow was performed using repeated ultrasonic measurement, however readings were difficult to reproduce for a variety of reasons – patient position, the turbulent flow inherent at the arteriovenous junction, compressibility of the venous component despite arterialisation, and inter-operator variability. Nevertheless, access flow measurements had minor relevance for the diagnosis of steal syndrome as, depending on the severity of arterial disease, symptoms can occur at any rate of access flow. This study did not have access to a dedicated vascular scientist and therefore in-depth arterial assessments or waveform analysis using doppler ultrasound could not be performed.

3.12 Discussion

Severe hand ischaemia as a consequence of arteriovenous steal is rare and seldom requires surgical intervention [110]. The incidence of steal phenomena is unknown; it is likely under-reported despite affecting a large proportion of patients on haemodialysis. This is possibly due to steal phenomena manifesting at a lower severity and therefore dismissed as a mild annoyance, bearable and not requiring intervention. As a result, few studies have solely focused on the occurrence of this phenomena.

In retrospect, utilising the Steal symptom score at 6 months as the primary endpoint was not ideal. Although it had previously been published, it had not been extensively validated. The sample size calculation was based on a previous unpublished pilot study that had estimated the expected incidence of steal in Intervention A and Intervention B to

be 30% and 5% respectively which was perhaps overly optimistic. To compound the issue, patient attrition in the form of thrombosed fistula, patient death or withdrawal of haemodialysis meant that these individuals were not included in the 6-month Steal symptom score analysis detailed in Section 3.10.1. The degree of attrition should have been factored into the sample size calculation to a greater extent. Instead, we should have considered a broader, more inclusive primary endpoint, using the grading system proposed by Tordoir et al [75], which mirrors the classification used in the grading of lower limb ischaemia.

In this study, the classification of each patient's ischaemic symptoms was not blinded. Nevertheless, our results demonstrate that a majority of patients dialysing via antecubital fossa fistula experience some degree of steal and this has not been widely appreciated in the published literature. Our data suggests that 73.5% of patients that were randomised to Intervention A had an element of steal phenomena (Grade 1-4), and 47.1% had more severe symptoms (Grades 2-4). In comparison, for Intervention B, 46.4% had elements of steal phenomena (Grades 1-4) with 10.7% having severe symptoms (Grades 2-4). In our entire cohort of patients, 19 (30.6%) had mild symptoms (Grade 1), which would not have ordinarily been picked up in scheduled dialysis sessions. A total of 38 patients (61.3%) experienced some degree of steal phenomena, albeit that this tended to be skewed towards the less severe side of the spectrum. From existing published series, the estimated incidence of symptomatic ischaemia ranges from 2-8 percent of the haemodialysis population [107]. In our cohort, 19 (30.6%) patients experienced more debilitating symptoms of steal, with 3 patients experiencing rest pain and/or tissue loss. In this study only 1 patient required operative intervention in the form of a RUDI to ameliorate severe steal.

The Steal symptom score was not particularly useful clinically as previously mentioned in the discussion in Chapter 2 – primarily because it assumes that all 5 variables are weighted equally, when in fact they represent a progression of ischaemic symptoms from coldness to weakness and altered sensation and finally to cramp and pain. This lends the possibility that patients with similar steal symptom scores might experience very different symptom severity, making it challenging to make any meaningful comparisons. The basis

of the steal symptom score is the visual analogue scale (VAS), which was initially developed to measure subjective phenomena such as emotion and mood [130]. It has since been employed as a measurement scale for several fields, most notably pain. While the VAS has been widely recognised as the most feasible and acceptable of health state evaluations, it does suffer from limitations – most notably a "ceiling effect". This can conceal variations in severity and/or intensity, causing compression of these ratings. In reality, the majority of patients reported within a narrow range of scores, making it difficult to ascertain any changes in their symptom severity over the course of the six-month study period [130,131]. At six months, there was no significant difference in the mean Steal symptom score in both cohorts, nor was there a significant difference in the subgroup scores (Figure 3.8 and Figure 3.9).

Recruitment of patients for the trial proved to be challenging. Despite identifying and recruiting all possible patients during the study interval where an antecubital fossa was deemed necessary, numbers remained small, with only one or two patients recruited per month. This resulted in several extensions to the study duration. The primary reason for this was the success of our radiocephalic fistula programme, which furnished individuals for functional distal fistulae with good patency, mean that patients requiring an antecubital fossa fistula would have necessarily exhausted all distal upper arm options. The net result was a small pool of suitable patients requiring an antecubital fossa fistula. Since the incidence of steal in proximal radial/ulnar fistulae is unknown whereas it is documented for brachiocephalic fistulae, there could be an argument for using an unequal allocation, perhaps 2:1 or 3:1. This might allow for more information on primary and secondary outcomes to be gained for the intervention [132]. However, unequal allocation would require the recruitment of a larger cohort to achieve the same level of statistical power [133]. The very same successes with our distal fistula programme led to the retrospective examination detailed in Chapter 4, where we challenged the premise that elderly individuals commencing haemodialysis would be better served with a brachial fistula rather than a fistula sited distally at the wrist.

The purpose of this trial was to investigate the hypothesis that patients with a fistula utilising the proximal radial/ulnar artery as arterial inflow (Intervention B) have a lower

incidence of steal symptoms compared to patients with a fistula using the brachial artery as inflow. From the demographic data in Table 3.1, both cohorts were comparable, with similar comorbidities. Despite this, the cohort randomised to Intervention B experienced a statistically significant reduction in steal symptoms as compared to patients randomised to Intervention A. This observation also held true when the cohort was reanalysed considering the actual intervention performed. The post-operative assessment of steal and its grading was based on clinical assessment and therefore is observer-dependent. Consequently, there might be unconscious observer bias. This was minimised firstly by asking the "blinded" patients to rate the severity of their symptoms on a visual analogue scale and secondly by performing the assessment prior to any ultrasonic examination, which would confirm the actual fistula created. Certainly, the data does support our hypothesis.

Preoperative measurements of digital pressures may help to identify patients at risk of developing steal. Patients that had low initial (preoperative) digital pressures / DBPI tended to develop more severe grades of steal (Figure 3.16), however there is no strict DBPI threshold below which steal is inevitable. During preoperative assessment, both randomised cohorts had similar DBPI, and certainly postoperatively we observed that patients randomised to Intervention A had lower DBPI as compared to those randomised to Intervention B (Figure 3.15). Overall, perhaps unsurprisingly, patients with lower postoperative DBPI experienced a greater severity of steal symptoms (Figure 3.15).

A vascular access surveillance programme utilising digital and brachial blood pressure measurements would present a low cost, highly effective way of identifying patients with steal phenomena and symptomatic steal, whereby early intervention could be considered to halt the progression to more severe symptoms. In Chapter 2, we had established using ROC curve analysis and Youden's J statistic that the optimum cut off DBPI for experiencing a clinical symptom of steal was 0.57. This finding appears to be supported in Figure 3.15, but larger cohort studies are required before a definitive answer can be provided. Each participant was monitored for 6 months after fistula creation, and therefore patients who developed ischaemic steal symptoms after the study period were

not formally captured in the study; we intend to report this data in once the study concludes.

During the study interval, six patients died or were withdrawn from haemodialysis. Whilst the decision to create an arteriovenous fistula is multidisciplinary involving nephrologists, vascular access nurses and access surgeons, it highlights the need for better markers or indicators to identify patients who are physiologically deteriorating, so that appropriate renal replacement therapy can be instituted.

This study has shed some light on symptomatic steal and steal phenomena which is currently underdiagnosed and therefore under-reported. Current diagnosis and treatment appear to be inadequate. Our results suggest that if several risk factors for steal are present pre-dialysis (diabetes, hypertension, ischaemic heart disease), particularly in the presence of low finger pressures, it would be prudent to consider the creation of a PRCAVF / PUCAVF fistula in preference to a BCF. When ischaemia is suspected, adequate diagnosis and timely intervention is necessary to avoid tissue loss. This study aims to generate more interest in this condition and foster a better understanding amongst physicians and surgeons alike – that we would be more vigilant in diagnosing steal and steal phenomena, and as a result, be able to keep these patients under surveillance and deliver better quality care to our patients, improving their lives for the better.

3.12.1 Further work

Patients were only followed up for a period of 6 months. As such, the longevity (primary/secondary patencies) of a proximal radial/ulnar fistula is yet to be determined; current data would suggest that it is comparable (Figure 3.17). Following completion of the study, the long-term patencies of these fistulae can be determined.

3.12.2 Novel Findings

In this chapter, I determine:

The incidence of steal phenomena and steal syndrome (grades 1-4) for patients with a BCF is 73.5%. For more severe symptoms (grades 2-4) the incidence is 47.1% (Section 3.10.2). The incidence of mild steal (steal phenomena) is unknown in current literature and the manifestation of moderate to severe symptoms in our cohort is much higher than has previously been reported in the literature. To my knowledge, this is the first report to classify incidence of steal according to grade of severity.

I establish that utilising the proximal radial/ulnar artery as arterial inflow for fistula creation results in significantly lower incidence of steal and steal phenomena. In our cohort, patients receiving Intervention B were less likely to experience the more debilitating symptoms of steal (Figure 3.10). The complications rates and 6-month fistula survival for both interventions are comparable (Sections 3.10.4 and 3.10.5).

I also identified that regardless of intervention performed, lower pre-operative DP / DBPI was likely to give rise to more severe grades of steal (Figure 3.13 and Figure 3.14). Similarly, as expected, the postoperative DBPI is inversely related to the grade of steal experienced; a low DPBI would suggest more severe symptoms (Figure 3.15). This relationship whilst obvious is not widely appreciated in the vascular access literature.

4 OUTCOMES OF PRIMARY ARTERIOVENOUS FISTULAE IN ELDERLY PATIENTS

4.1 Introduction

As the population ages, the incidence of end-stage renal failure (ESRF) is increasing [134], resulting in more elderly patients being considered for haemodialysis. More than 80% of all patients worldwide who receive treatment for renal failure live in affluent countries with good access to healthcare and large elderly populations [135]. It is estimated that one in five men and one in four women between the ages of 65 and 74, and half of people over the age of 75 have chronic kidney disease [136]. In the UK, the median age of the incident haemodialysis population has increased from 61 in 1997 to 66.9 in 2012, and in 2000, 19.2% of haemodialysis patients were older than 70, whereas for 2012 that figure is 24.9% [137,138].

Provision of vascular access in elderly haemodialysis patients is undoubtedly challenging, with relatively little data published to inform decision making [45,117,134,139–142]. Current guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI), the Society of Vascular Surgery, and the United Kingdom Renal Association [20,143,144] do not distinguish elderly haemodialysis patients as a separate cohort. All recommend that in order to preserve proximal sites for future access attempts, arteriovenous fistulae are sited as distally as possible in the upper extremity, with the implication that where possible, radiocephalic fistulae should be performed as first choice for dialysis access in the elderly. Nevertheless, on the basis that preservation of venous capital is less of a concern due to the limited life-expectancy of elderly haemodialysis patients, allied to the consideration that patency rates for radiocephalic fistulae in this cohort may be lower [45,117], several authors have advocated that antecubital (brachiocephalic (BC) and brachiobasilic (BB)) fistulae should instead be considered the first option [45,145,146]. Complication rates for antecubital fistulae are, however, higher than for wrist fistulae, and in particular, the incidence of hand ischemia from steal syndrome is approximately ten-fold higher for fistulae created in the antecubital fossa [73,75,76]. Similarly, survival rates for elderly dialysis patients are improving [147]. Hence, consensus as how to best provide haemodialysis access for elderly patients with ESRF has not been reached [148].

On the basis that fistulae formed using small veins are less likely to mature [149–151], many centres create radiocephalic (RC) fistulae only if the cephalic vein is at least 2.5mm

or 3mm in diameter. However, this generally results in the majority of fistulae being sited in the antecubital fossa [37,152,153]. In comparison, our strategy for vascular access provision has focused on maximizing the numbers of RC fistulae created. Irrespective of vessel size, we create a RC fistula if the radial artery and cephalic vein at the wrist are judged clinically suitable [104,154]. Using this strategy, we fashion RC fistulae in over 80% of patients, with one year patency rates of 77% [154]. We adopted the same approach for provision of permanent vascular access in elderly haemodialysis patients, principally because of concerns that antecubital fistulae would carry a higher risk for development of steal syndrome. Here we report a large single centre retrospective cohort study describing provision of vascular access surgery for haemodialysis patients aged over 70. Contrasting previous reports [117], RC fistulae were created successfully in the majority of patients, with acceptable maturation and patency rates and with a low incidence of complications.

4.2 Methods

4.2.1 Patients

All consecutive patients aged 70 and above who had a primary arteriovenous fistula created between 1st January 2005 and 31st Dec 2012 in Addenbrooke's Hospital were identified from our prospectively maintained vascular access database. All cases were retrospectively cross-referenced to theatre records. Incident haemodialysis patients who had a primary RC, BC or BB fistula created as their first option for permanent haemodialysis access were included in the analysis. No prosthetic grafts were used as first-line vascular access in our cohort.

Case notes were examined for operative details. Data was analysed until cessation of follow-up on 30 June 2013.

4.2.2 Preoperative assessment and initial AVF creation

Our unit has previously demonstrated that clinical examination can suffice in certain instances [154]. Patients underwent preoperative clinical assessment, with Doppler ultrasound (FUJIFILM SonoSite^{TM}) performed as an adjunct to clinical examination. In

these cases, the diameters of the vessels of interest were recorded. In accord with our previous publication [154], we did not employ a threshold value for the diameter of the wrist cephalic vein below which a radiocephalic fistula was not attempted, and were prepared to create fistulae with cephalic vein diameter less than 2.5mm if the vein was deemed clinically to be of good quality [154]. Where clinically indicated, patients thought at risk of central venous stenosis were imaged preoperatively using magnetic resonance or computerised tomography. Fistulae were created by a consultant surgeon with a special interest in vascular access and a team of transplant registrars. Both primary fistulae and proximal revisions were performed by the same team.

4.2.3 Description of surgical technique

Almost all fistulae were created under local anaesthetic, with exception of BB fistulae, which were created as a single stage procedure under general anaesthesia. Heparinised saline was used to distend the vein prior to anastomosis, and an end-to-side anastomosis was created with 6-0 or 7-0 prolene. Antiplatelet agents (generally aspirin) were continued in the postoperative phase. Radiological salvage of a failed radiocephalic fistula was not available during the study period; secondary patency rates therefore reflect only operative salvage through formation of a proximal neo-anastomosis [104].

4.2.4 Outcome and statistical analysis

Patients who had an arteriovenous fistula created but did not proceed to require haemodialysis were excluded from further analysis. Categorical variables were compared using Fisher's exact test. Kaplan-Meier survival analyses and Log-rank tests were used for fistula survival and for patient mortality. Kaplan-Meier analysis was performed on an intention to treat basis, as outlined by Sidawy et al [30]; fistulae that failed within 72 hours were deemed to have failed at time zero. All analyses were performed with GraphPad Prism (v.5.03 GraphPad Software Inc, CA, USA). Patients were censored in the event of death or final measurement of patency.

4.3 Results

4.3.1 Patient Cohort

Between 1st January 2005 and 31st December 2012, 304 patients aged over 70 were referred for creation of permanent haemodialysis vascular access. At referral, 52.3% of patients were pre-dialysis; the remainder were dialysing via a central venous catheter (CVC). Patient demographics of those that commenced haemodialysis during the study period are detailed in Table 4.1: 67.8% of patients were male, 67.8% were receiving anti-hypertensive medication, and 24.3% were diabetic.

	Primary RC fistula (n = 204)	Primary antecubital fistula (n = 10)	P value[c]
Age (years)[a]	78 (4.92)	76 (4.49)	0.35[d]
Gender *male* (%)[b]	141 (69.1)	4 (40.0)	0.08[e]
Anastomosis site	204 RC	9 BC 1 BB	
Hypertension (%)	139 (68.0)	6 (60.0)	0.73[e]
Diabetes (%)	49 (24.0)	3 (30.0)	0.71[e]
Predialysis (%)[b]	67(32.8)	2 (20.0)	0.51[e]

Table 4.1: Patient Characteristics

RC, radiocephalic; BC, brachiocephalic; BB, brachiobasilic

[a] Values are mean (SD); [b] Patients already established on dialysis were dialyzing through central venous catheter [c] Comparison made between RC and BC fistulae [d] Mann-Whitney U test; [e] Fisher's exact test

4.3.2 Provision and Outcomes of Haemodialysis Access Surgery

As detailed in Figure 4.1, of the 304 primary access procedures performed, 293 (96.4%) RC and 11 (3.6%) antecubital (10 BC and 1 BB) arteriovenous fistulae were created; no arteriovenous grafts were formed. Ninety (29.6%) patients remained pre-dialysis and were excluded, leaving the remainder (204 RC, 9 BC, 1 BB fistulae) as a cohort for further analysis. Patency rates for these fistulae are detailed in Table 4.2, which shows that primary maturation rates and one-year primary patency rates were similar for RC and BC fistulae, albeit direct comparison is difficult due to the small number of BC fistulae created as a primary procedure. Twenty-five RC and two BC fistulae experienced immediate failure (12.3% and 22.2% respectively, P = 0.319, Fisher's exact test).

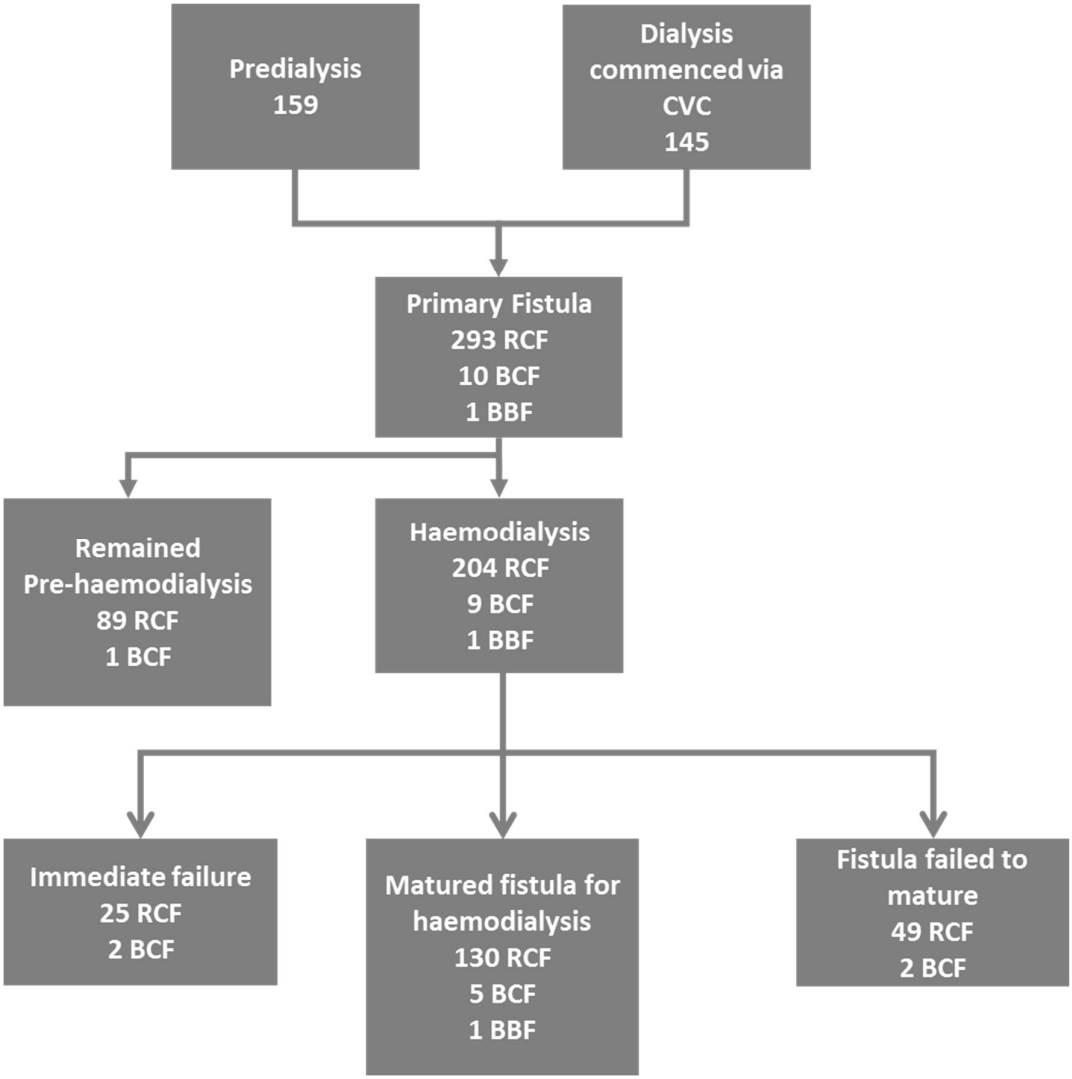


Figure 4.1: Outcome of patients over 70 referred for creation of permanent haemodialysis access.

RCF, radiocephalic fistula; BCF, brachiocephalic fistula; BBF, brachiobasilic fistula

	Primary RC fistula (n = 204)	Primary antecubital fossa fistula (n = 10)	
		BC (n = 9)	BB (n = 1)
Achieved maturity and subsequently used for dialysis (%)	130 (63.7)	5 (55.6)	1
Immediate failure (%)	25 (12.3)	2 (22.2)	0
Median primary patency in months (range)	12.9 (0-97.4)	5.3 (0-47.1)	2.8
Median secondary patency in months (range)	33.4 (0-97.4)	6.7 (0-47.1)	2.8

Table 4.2: Patency rates of patients who proceeded to haemodialysis

RC, radiocephalic; BC, brachiocephalic; BB, brachiobasilic

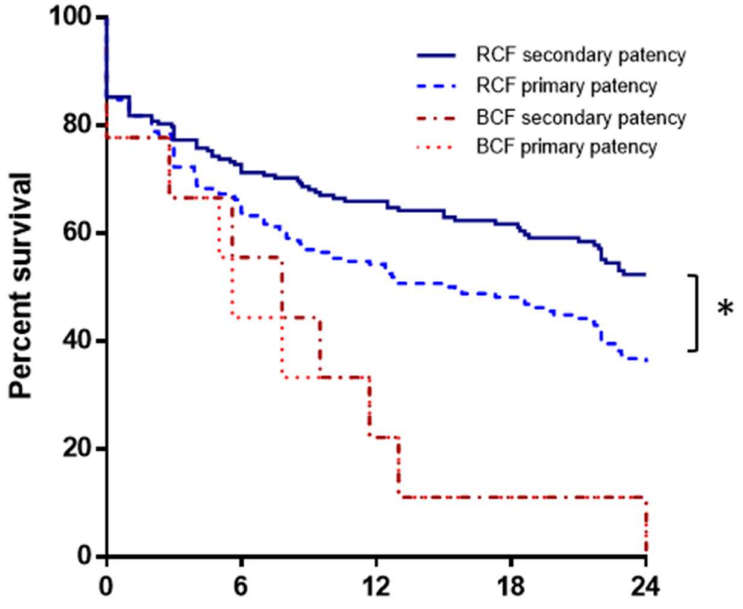
For those patients whose fistula failed to mature (49 RC and 2 BC fistulae, 24.0% and 22.2% respectively), subsequent access interventions are detailed in Table 4.3. Eight patients with RC fistulae declined further fistula creation and elected to dialyse via a central line. Operative salvage was attempted in 18 RC fistulae that had failed to mature, by creating a more proximal neo-anastomosis [104]. This proximal revision was successful in 15 patients. During the study period, a further 33 wrist fistulae that had achieved functional patency were salvaged successfully upon failure by formation of a proximal neo-anastomosis. As a consequence of early and late operative salvage of failed RC fistulae, one-year secondary patency rates for wrist fistulae were significantly higher than primary patency rates (66.0% vs 54.3%, P = 0.027, Log-rank test, Figure 4.2).

Subsequent access interventions	Failed to achieve maturity (number)	
	Radiocephalic fistulae (49 of 204)	Brachiocephalic fistulae (2 of 9)
Proximal neo-anastomosis	18	0
Refused further surgery	8	0
Further primary wrist fistula	12[a]	2[b]
Further primary brachiocephalic fistula	11	0

Table 4.3: Outcome of fistulae which failed to achieve maturity

[a] 7 contralateral radiocephalic fistulae, 3 ipsilateral ulnarbasilic fistulae and 2 ulnarcephalic fistulae

[b] 2 ipsilateral radiocephalic fistulae



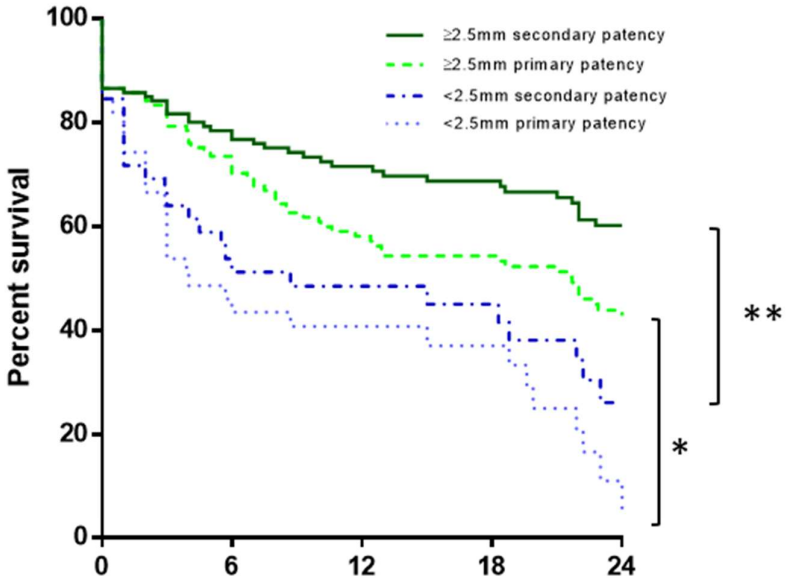
Numbers at risk					
RCF (secondary patency)	204	141	116	96	73
RCF (primary patency)	204	126	95	75	52
BCF (secondary patency)	9	5	2	1	1
BCF (primary patency)	9	4	2	1	1

Figure 4.2: Survival of radiocephalic (RC) and brachiocephalic (BC) fistulae

*** For radiocephalic fistulae, one-year secondary patency rates were higher than primary patency rates (P = 0.027, Log-rank test).**

4.3.3 Effect of cephalic vein diameter on fistula patency

Our approach to haemodialysis provision differs from other centres in that we do not adopt a minimum cut-off value for the diameter of the cephalic vein, below which a radiocephalic fistula is not attempted. Pre-operative ultrasound measurements of the diameter of the cephalic vein were recorded for 166 of the 204 wrist fistulae created (81.4%), and of these, 39 (23.5%) had radiocephalic fistulae formed using cephalic veins less than 2.5 mm in diameter. Although immediate failure rates of these fistulae were comparable for radiocephalic fistulae created using cephalic veins greater than 2.5mm in diameter (15.4% vs 13.4%, P = 0.79, Fisher's exact test, Figure 4.3), one year primary patency was poorer (40.9% vs 58.2%, P = 0.015, Log-rank test, Figure 4.3). As a result of salvage through formation of a proximal neo-anastomosis, secondary patency rates were greater, albeit still poorer than was achieved for fistulae created using cephalic veins ≥2.5mm (48.6% and 71.6%; P = 0.005, Log-rank test, Figure 4.3).



Numbers at risk

≥ 2.5mm (secondary patency)	127	93	78	66	52
≥ 2.5mm (primary patency)	127	85	63	53	40
< 2.5mm (secondary patency)	39	20	15	13	6
< 2.5mm (primary patency)	39	17	12	10	2

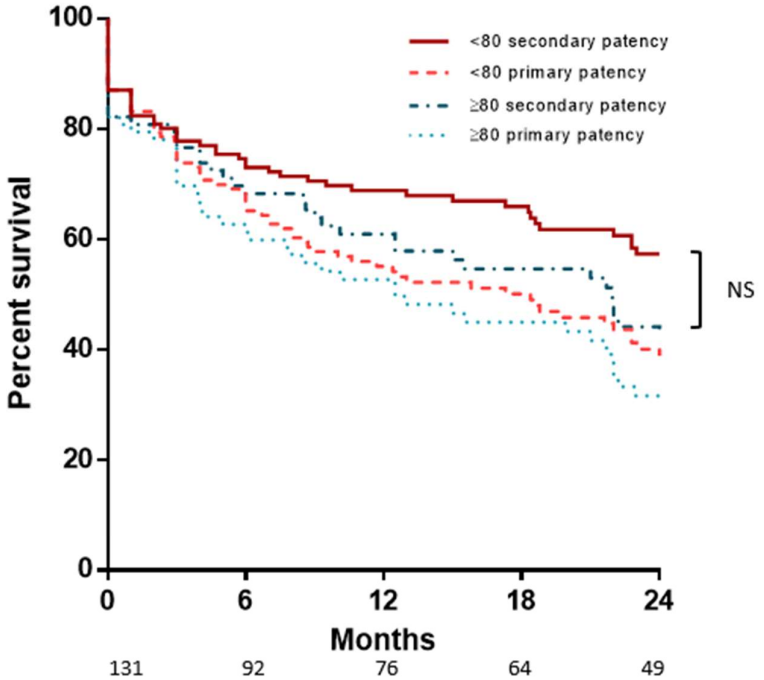
Figure 4.3: Patency of radiocephalic fistulae stratified according to cephalic vein (CV) size

*** Primary patency at one year was poorer in radiocephalic fistulae utilizing CV <2.5mm as compared to those with CV >2.5mm (P = 0.015, Log-rank test)**

**** Secondary patency rates of radiocephalic fistulae created with CV <2.5mm was poorer than those using CV>2.5mm (P = 0.005, Log-rank test)**

4.3.4 Patient age and fistula patency

Although the immediate failure rates of radiocephalic fistulae formed in patients aged between 70 and 80 was lower than those formed in patients over 80 years old, this was not statistically significant (9.9% vs 16.4%, P = 0.19, Fisher's exact test, Figure 4.4). Two-year secondary patency rates for these groups were also not statistically different (57.3% vs 44.2%, P = 0.114, Log-rank test, Figure 4.4).



Numbers at risk

<80 (secondary patency)	131	92	76	64	49
<80 (primary patency)	131	82	60	48	33
≥80 (secondary patency)	73	49	40	32	24
≥80 (primary patency)	73	44	35	27	19

Figure 4.4: Primary and secondary patency of radiocephalic fistulae stratified according to age

*** Two-year secondary patency for these groups were not statistically significant (P = 0.066, Log-rank test).**

NS, not significant

4.3.5 Establishment of haemodialysis

As can be seen from Table 4.4, which reports the dialysis mode one year after creation of the first radiocephalic fistula, 69.6% of those patients which were dialysing did so via a wrist fistula, with a relatively low percentage (24.3%) dialysing via a central line. Thus, despite an immediate failure rate of >30% for wrist fistulae in the elderly, the additional salvage operations required (mean 1.38 per patient) do not appear to lead to delays that ultimately increase the reliance on dialysis via a central line. As additional support, of the 159 pre-dialysis patients that underwent autogenous fistula formation, 69 (67 RC + 2 BC fistulae; 43.4%) proceeded to require haemodialysis during the study period. Of these, 65 (94.2%) avoided central line catheterisation and initiated haemodialysis via their fistula, with a median time of 8 months (range 0-60) from referral to initiating dialysis.

Disposition	n	%
Radiocephalic fistula	82	40.2
Tunneled central line	36	17.6
Predialysis	29	14.2
Proximal radiocephalic fistula	20	9.8
Death	18	8.8
Brachiocephalic fistula	9	4.4
No longer required dialysis	8	3.9
Ulnarcephalic fistula	1	0.5
Dialysis discontinued (subsequent death)	1	0.5

Table 4.4: Outcome and dialysis mode 1 year after creation of primary radiocephalic fistula

4.3.6 Complications and Patient Mortality

One of the major concerns underlying our strategy of focusing on the creation of distal (radiocephalic) fistulae was the potential for development of steal syndrome following formation of antecubital (BC and BB) arteriovenous fistulae in the elderly. A total of 298 vascular access procedures were performed on the elderly dialysis cohort during the study period (214 primary and 84 secondary procedures). Only nine patients developed steal syndrome; in eight this required either ligation of their fistula or a revision using distal inflow (RUDI) procedure [88,89]. One further patient described marked hand claudication, associated with a systolic digital blood pressure of 54mmHg – this was treated conservatively. In agreement with published literature [73,74], steal syndrome developed much less frequently following formation of a wrist, than elbow, fistula (5 of 51 (9.8%) for antecubital (BC and BB) fistulae and 4 of 247 (1.6%) for RC fistulae; P = 0.009, Fisher's exact test, Odds ratio 6.60).

An additional consideration influencing the decision to site an AV fistula more proximally is the anticipated improved immediate patency rates in a dialysis population with limited life expectancy. Only 3 patients from our study population received a transplant. For the rest of the study population, in keeping with recent UK Renal Association data [155], survival was perhaps better than anticipated (Figure 4.5); at commencement of dialysis, of the patients aged 70 to 80, and those over 80 years, 53.9% and 46.3%, respectively, were alive four years later.

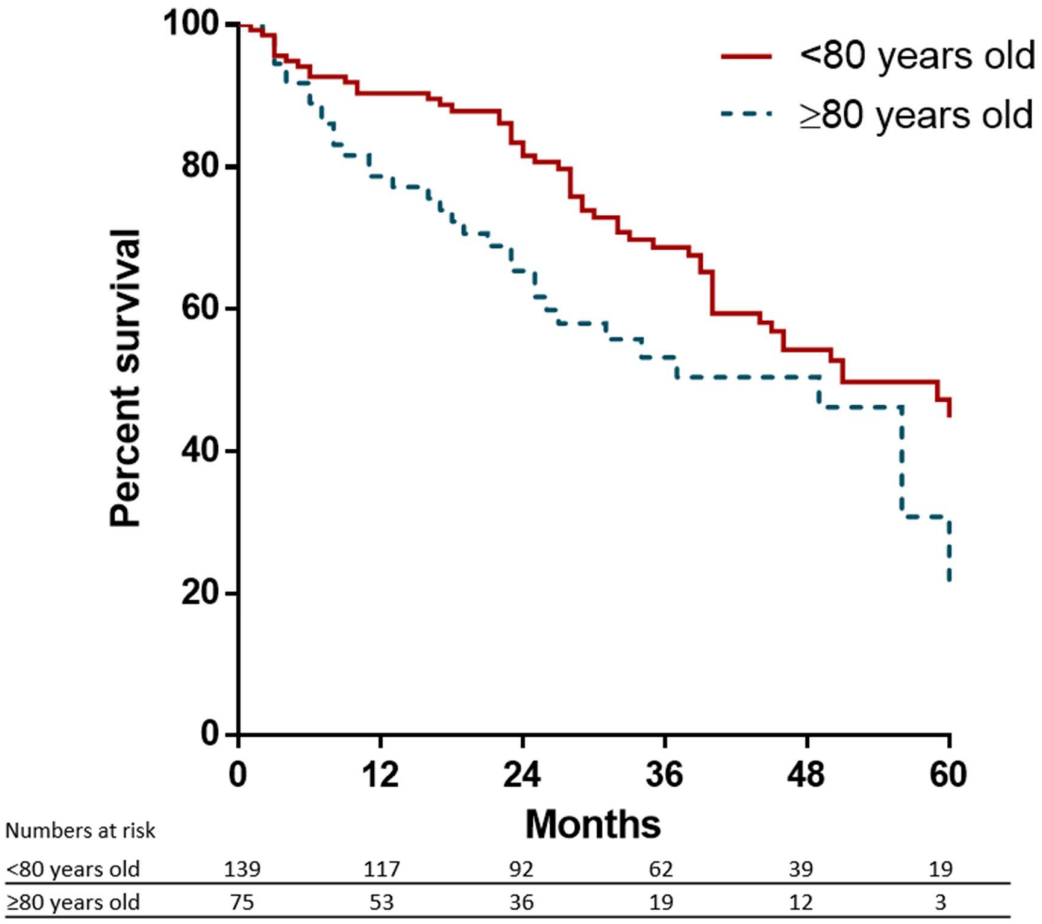


Figure 4.5: Kaplan-Meier analysis for patient survival according to age from commencement of dialysis

As expected, survival outcomes were statistically significant between these 2 groups (P = 0.035, Log-rank test)

4.4 Limitations

This was a single-centre retrospective cohort study examining access outcomes. The cohort examined was predominantly Caucasian. As such, the sample population might not be entirely representative of the UK population at large. Furthermore, as a retrospective study, it come with all the limitations this this connotes.

4.5 Discussion

The best choice of permanent access procedure for elderly haemodialysis patients remains controversial [45,117,134,141,142]. Selection is based upon a number of competing factors such as: patient life expectancy; expected immediate patency rates; and risk of complications [141,156,157]. In this study, one of the largest series to date reporting outcomes for haemodialysis patients over the age of 70, we highlight that successful access placement can be achieved using an approach predominantly focused upon creation of RC fistulae. Creation of wrist fistulae in the elderly is not a novel concept, but perhaps the most important aspect of our study is that approximately 70% of our elderly patients successfully dialyse via a RC fistula. This represents a much higher proportion than reported in other publications detailing outcomes for elderly haemodialysis patients [156,158] and indeed, is higher than is typically reported by centres for their entire haemodialysis population [153,159,160].

Nationally, unadjusted 4-year survival for incident haemodialysis patients aged ≥65 as reported in 2012 was 40.9% [155], and historically the median survival for very elderly patients (>75 years) is less than 2 years from initiation of dialysis. In comparison, our elderly haemodialysis cohort aged ≥70 had a better than predicted survival, with 51.2% alive at 4 years. Thus, survival of the elderly dialysis population appears to be improving, suggesting that greater emphasis should be placed on conserving proximal access sites for future access provision.

Our results suggest that for elderly patients with wrist cephalic veins greater than 2.5mm, creation of a radiocephalic fistula should be the first option assuming suitable arterial inflow. Such an approach would be anticipated to achieve reasonable patency rates and

to be associated with minimal complications, and in particular to carry a low risk for development of steal syndrome. This strategy moreover, provides the additional advantage of successful salvage and preservation of venous capital; it is notable in our series that the formation of a neo-vascular anastomosis improved 1 year patency rates by 12%.

The most appropriate choice for fistula placement in those patients with small cephalic veins (<2.5mm) who are nevertheless felt to have reasonable vein quality is more contentious. The immediate failure and primary patency rates for wrist fistulae created in these conditions were undoubtedly poor, with less than half achieving primary patency at one year. Nevertheless, secondary patency rates were acceptable and substantially better than the secondary patency rates for elbow fistulae created. It should however be emphasised that very few antecubital fistulae were performed as a primary procedure, and direct comparison between outcomes for elbow and wrist is therefore difficult, Moreover those patients in our study selected for brachiocephalic fistula as the first option for haemodialysis provision were generally considered to have poor quality radial artery or cephalic vein at the wrist and are perhaps a cohort selected to have inherently poor results for haemodialysis access provision. Nevertheless, it is undoubtedly more difficult to surgically salvage failed brachiocephalic than radiocephalic fistulae [146], which may partly explain why one year secondary patency rates were relatively poor for BC fistulae, despite the immediate patency rates being similar to those achieved for RC fistula. We do not routinely attempt radiological salvage of a failed BC fistula, because our experience mirrors reports from other centres [50,161–163], in that improvements in fistula patency are only achieved by intensive and repeated radiological intervention.

Accepting the above limitations with the analysis of outcomes for brachiocephalic fistula in our study, our findings, at the very least, raise questions as to the merits of an approach in elderly patients centred predominantly upon creation of elbow fistulae. Indeed, it would be difficult, given the high incidence of steal associated with elbow fistulae in our series, to justify such a change in our practice without performing a prospective trial in which elderly patients with small (<2.5mm) wrist cephalic veins that are deemed clinically usable are randomised to either radiocephalic or brachiocephalic fistulae. End

points would include: immediate failure rates; one and two-year patency; and development of clinically relevant steal.

Finally, it is surprising that formation of proximal neo-anastomosis was reasonably successful in salvaging wrist fistulae which failed to mature, supporting the contention that the radial artery and cephalic vein at the wrist were of sufficient quality to attempt radiocephalic fistula creation, but that there are perhaps stochastic events that influence successful maturation. The neo-anastomosis was routinely performed just proximal to the initial anastomosis and it is therefore unlikely that the arterial and venous calibre differed significantly at the second anastomotic site. We are however careful to counsel patients regarding the relatively high risk of primary failure and that a secondary procedure may be required.

4.5.1 Novel Findings

In this chapter, I have demonstrated that:

Successful radiocephalic fistula placement can be achieved in an elderly population and in our cohort approximately 70% dialyse via this modality. As outlined above, this represents a much higher proportion than in other publications outlining dialysis outcomes for their elderly population.

I also show that, for our cohort, four-year survival is better than expected. This could either reflect the generally higher socioeconomic status of the catchment area and consequently better health than the national average, or suggest that survival of the elderly dialysis population is improving. This improved survival suggests that, at least for our cohort, a greater emphasis should be placed on conserving proximal access sites for future access provision.

5 CONCLUSIONS

5.1 Conclusions

Over the past decade, there has been an incremental growth of patients with end-stage renal failure on chronic haemodialysis. It is estimated that 10% of the population worldwide is affected by chronic kidney disease; over 2 million people worldwide currently receive treatment via dialysis or transplant, and this may only represent 10% of the actual population requiring renal replacement therapy [135,136]. Costs and complications have become increasingly significant components in the management of these patients. Ensuring functional vascular access is of paramount importance to not only the patient, but also to healthcare staff and the haemodialysis unit. An optimal access is one which provides long term patency, delivering adequate blood flow for efficient haemodialysis without associated complications. A structured surveillance programme allows for early identification of a failing access, allowing for prompt intervention and thereby increasing the overall lifespan of the vascular access. Similarly, prospective monitoring of an arteriovenous fistula could provide early detection of steal phenomena and allow for possible early intervention, thereby possibly preventing debilitating rest pain and tissue loss.

Current guidelines published by the NKF-KDOQI, UK Renal Association and European Society for Vascular Surgery recommend that upper limb distal autogenous fistulae (RCF) should be created in the first instance, followed by more proximal fistulae (BCF/BBF) [20–22]. Should this not be possible, a prosthetic graft or tunnelled CVC should be considered. Some authors have suggested that a blanket “fistula first” approach to access creation in the elderly may be detrimental given the time taken for an autogenous fistula to reach maturity, in addition to the multiple comorbidities and high patient mortality in this group [148,164,165]. Whilst this aspect might be true, it only highlights the importance of ensuring that a functional fistula is in place prior to being required. Guidelines advise early referral at least 3-6 months prior to the anticipated commencement of haemodialysis, allowing for AVF creation and subsequent maturation, as well as possible interventions to aid in the maturation process. Late referral for AVF creation risks potential non-maturation, being unsuitable for initiating haemodialysis, and need for CVC or prosthetic graft placement. Both CVCs and grafts have higher rates of infection. What is also true is that prosthetic grafts have a higher reintervention rate to maintain functional patency, and this also has an impact on the patient’s quality of life [148].

The importance of "getting it right from the start" is critical. Initial decisions about vascular access modality have long term ramifications for patients and implications as to their time spent on dialysis. In recent years, there has been a drive towards a tailored "patient-centred approach" [123,141,166], with a reframing of the "fistula first" ideal to that of the "catheter last" [106,167]. To achieve this, proposed strategies include early identification of patients requiring vascular access, tailored fistulae taking into account expected patient life expectancy and potential failure rate [168,169], as well as implantation of early cannulation grafts [170,171]. Patients initiating dialysis via a central venous line are more likely to continue dialysing via line. Data from the UK renal registry indicate that 60% of patients starting on a tunnelled line continue to dialyse via line at 3 months and >40% still dialyse via this modality at 1 year [65]. In this respect, Addenbrookes continues to be one of the leading centres in the UK where at 3 months from commencement of dialysis, almost half (48.6%) of all patients dialyse via AVF, with the national average being 27.7% [65].

The focus of this thesis has been the examination of the manifestation of steal phenomena and steal syndrome in patients with autogenous arteriovenous fistulae. Within this thesis three themes have been explored:

1. Digital finger pressures and its correlation to steal phenomena and steal syndrome
2. Reduction of steal symptoms by means of utilising a distal arterial inflow
3. Elderly patients initiating dialysis should still be considered for formation of a distal radiocephalic fistula

Chapter 2 details the role that digital pressure has in identifying patients at risk of developing arteriovenous access ischaemic steal. Specifically, I demonstrate that patients with low brachial pressures tended to have corresponding lower digital pressures and were more symptomatic. This relationship has not been previously recognised in the literature. My data suggests that for individuals who experience debilitating steal, formation of an identical fistula on the contralateral side was just as likely to result in steal and should not be pursued, as the distal vasculature was likely to be comparable. I also establish that DP and DBPI can be used as a sensitive measure for detecting and predicting steal syndrome, with a DP of <65mmHg or DBPI <0.57 as the optimal point at which a patient is likely to have a positive clinical examination for steal. Further non-

invasive testing with digital pressure measurements and derivation of the digital brachial pressure index may help in the diagnosis and decision-making process. This has particular relevance in satellite or rural haemodialysis units where there is limited clinician availability and would serve as a quantitative means for non-clinical staff to identify patients at risk of developing steal.

In our cohort, 28.3% of patients had at least one clinical sign of steal syndrome, which was not anticipated, given that current published literature suggests that the incidence of steal is approximately 5% [71]. This implies that the incidence of mild steal symptoms is under-reported, or perhaps under-appreciated. Whilst this represents a significant proportion of our cohort, none of these individuals experiencing AVAIS required surgical intervention.

I established that there was poor linear correlation between the Steal symptom score proposed by van Hoek et al [110] and DP / DBPI. Disappointingly, it did not offer a means to stratify symptom severity, making it difficult to draw any meaningful conclusions when comparing patients with varying Steal symptom scores. Instead, the classification system proposed by Tordoir and Scheltinga [71,75] proved to be more valuable for making comparisons. We recommend that this grading system should be used in clinical practice and when reporting outcomes.

Chapter 3 outlines the results of an ongoing single-blinded randomised trial comparing the incidence of steal symptoms in antecubital fossa fistulae utilising different arterial inflows. We report the incidence of steal according to grade of severity and demonstrated that patients receiving haemodialysis via antecubital fossa fistulae experience a greater incidence of steal phenomena (66%) than has previously been reported in the literature. This result was significantly greater than the proportion (28.3%) exhibited in Chapter 2, which examines patients dialysing via all autogenous fistula modalities. In our cohort, 30% had moderate to severe symptoms, which is greater than what has been previously reported. The proportion of patients with moderate to severe symptoms which then progress to require surgical intervention remains uncertain, and would be the basis for further longitudinal studies.

Regardless of intervention performed, a lower pre-operative DP / DBPI was likely to give rise to more severe grades of steal. This relationship is not widely appreciated in the current vascular access literature. Greater dissemination of this association would help clinicians ascertain each individual's potential risks of steal syndrome and inform the consent process. We thus recommend that all patients undergoing autogenous fistula creation, and in particular patients receiving an antecubital fossa fistula, should have their preoperative DP and DBPI measured.

Patients who received Intervention B (proximal radial/ ulnar artery inflow) demonstrated significantly less incidence of severe steal, and less steal symptomatology overall. We demonstrated that both interventions had comparable 6-month fistula survival and that there was no difference in 6-month fistula outcomes (functional, thrombosed, failure to mature and other). Given the above, our findings are compelling and certainly has effected a change in our clinical practice, where patients with multiple risk factors for steal (diabetes, hypertension, ischaemic heart disease) have a PRCAVF / PUCAVF created in preference to a BCF. Nevertheless, we also established that severe digital ischaemia due to steal which required intervention was a rare entity, with only one patient in our cohort requiring surgery. Given the above findings, our recommendation is to consider formation of a PRCAVF / PUCAVF in preference to a BCF, particularly if risk factors for steal and low finger pressures are present.

Examination of the total Steal symptom score at 6 months did not reveal a significant difference in both interventions; this also held true when examining the individual parameters which comprise the score. As discussed above and in Section 3.12, this is perhaps due to each component being given equal weightage when in fact they represent progression of ischaemic symptoms. No linear correlation between score and symptoms was found, and therefore the score has limited clinical value and should not be used in routine clinical practice.

Identifying patients which required placement of an antecubital fossa fistula proved to be challenging. This was primarily due to the successful implementation of our radiocephalic fistula programme, which created functional radiocephalic fistulae which could sustain dialysis. In effect, we were a victim of our own success. The protracted

patient recruitment process necessitated several extensions to the projected trial end date. This recruitment obstacle led to the exploration detailed in Chapter 4, which challenges the notion that elderly patients should have proximal fistulae sited routinely.

Moving forward, valuable lessons were learnt in the inception, organisation and administration of this randomised controlled trial. We should have identified that the lengthy study duration would be a significant issue and taken steps to address this. The length of study and funding issues precluded the recruitment of a singular trial coordinator, which would have been invaluable. An alternative solution would have been enlisting the help of other centres, which would have necessitated amendments to the ethical approval, "buy-in" from the other centres, more staff and appropriate funding to be in place. These are important lessons which can be applied to further trials.

In Chapter 4, I report the outcomes for elderly incident haemodialysis patients at our institution utilising a retrospective analysis, highlighting that successful dialysis access can be achieved despite employing a strategy with favours radiocephalic fistula placement. This is in contrast to the current accepted dogma that elderly patients should have proximal (antecubital fossa) fistulae created in order to reduce the risks of non-maturation. My results show that approximately 70% of our elderly cohort dialysed successfully via RCF, which represents a higher proportion than reported in other publications and other centres for their entire haemodialysis population. The results also suggest that as long as the distal cephalic veins are larger than 2.5mm, reasonable patency rates are achievable for RCFs given suitable arterial inflow. This is in agreement with a systematic review examining cephalic vein and radial artery diameter in RCF formation, which suggests that the minimum radial artery and cephalic vein diameter is 1.5mm and 2.0mm respectively [172]. Below this threshold, maturation and primary patency rates of RCFs are poor. We also demonstrated that complication rates, including the dreaded steal syndrome, for distal fistulae are exceedingly low.

In contrast to other authors, our results suggest that patient age should not factor into vascular access strategy [120,139,141,148,173]; rather, projected life expectancy should be the measured variable instead. Our results in Chapter 4 demonstrate that for patients over the age of 80 initiating haemodialysis, 46.3% were alive four years later. Advanced

age is merely used as a surrogate for diminished life expectancy and multiple comorbidities. Projected life expectancy is understandably a nebulous concept that is difficult to quantify and reach agreement on, but nonetheless this is an important distinction to make. Given our results, we suggest that in elderly patients with anticipated longer life expectancies, a greater emphasis should be placed on conserving proximal access sites in preparation for future access provision. For individuals with an anticipated short life expectancy an autogenous fistula might not be the ideal choice for vascular access and indeed there should be a discussion of whether initiation of haemodialysis would improve the patient's quality of life or extend life expectancy significantly.

Given the chronic nature of renal failure, patients are unlikely to have a single form of vascular access, and over the course of their life receive renal replacement via a combination of fistulae, catheters, grafts, peritoneal dialysis and/or renal transplants. The most suitable access for a patient remains one that integrates individual circumstances and projected haemodialysis duration, whilst also considering patient comfort, satisfaction, quality of life and clinical outcomes. Patients should receive uninterrupted use of the access with minimal need for intervention and this would allow for the prescribed dialysis regimen to be received with minimal disruption. We have demonstrated that at our institution, we are able to create successful autogenous AV fistula in the majority of our patients, delivering effective haemodialysis.

Each access surgeon's training, skill, experience and outcomes will be different. Fistula outcomes are also dependent on institutional factors such as the availability of a vascular scientist, interventional radiology support as well as dialysis centre expertise. Our results show that establishing and maintaining autogenous access is attainable for most patients and should be vigorously pursued. In addition, understanding surgeons' preferences, values and beliefs around AVF eligibility is important to explain variability in practice [123]. Significant variability remains in surgical preoperative assessments and the eligibility criteria used for fistula creation. In a survey of vascular access surgeons performed by Nica et al [123], absolute contraindications to AVF creation included life expectancy of <1 year, left ventricular ejection fraction of <15% and pre-existing dementia. Increased comorbidities, small vessel diameter and previous failed access were deterrents to AVF creation.

5.2 Future trends in haemodialysis

Determining the optimal time to create an arteriovenous fistula or factors which can predict the progression to ESRF remains a challenge [156,174]. No current clinical practice guideline exists to drive rapid placement of definitive access amongst late presenting individuals; responsive dialysis access pathways involving prompt assessment by a nephrologist and rapid referral to a dialysis access surgeon should be prioritised. There remains considerable UK wide variation in access modality provision despite adequate infrastructure in place to support delivery of quality vascular access [175].

The rate of renal function deterioration appears to be an important factor in determining the optimal time for AVF creation [176]. As the rate of renal function decline is unpredictable, early creation of an AVF might not necessarily be the optimal strategy for pre-dialysis patients with a slow rate of renal deterioration, and a better understanding of the factors involved and better risk models are required [139]. It has also been suggested that very early AVF creation in the elderly cohort might expose patients to unnecessary operations and interventions in the event of death prior to requiring haemodialysis [141,176]. To that end, the kidney failure risk equations proposed by Inston et al [177] which estimates the probability of the 2- and 5-year risk of reaching end stage kidney disease shows promise, but further validation studies are required. Future studies evaluating the timing, modality of vascular access, considering complications, functionality, as well as patient preference are required, in order that optimised care can be provided and quality of life maintained.

What also remains to be addressed is the optimal access strategy for “crash landers” – patients who require immediate renal replacement upon presentation. For this cohort of patients requiring urgent dialysis, fistula placement often follows CVC line insertion. In this respect, early cannulation grafts certainly do show promise as an alternative to tunnelled CVCs for patients requiring urgent vascular access. Bacteraemia rates appear to be lower, and mortality rates are similarly superior [61,62]

Maturation times and fistula failure continue to present significant obstacles to successful fistula utilisation. Effective solutions require an appreciation of the modes and pathology of access failure which is still poorly understood [49,178]. A multidisciplinary approach

involving nephrologists, access surgeons and radiologists, coupled with appropriate patient selection and tailored treatments should improve patient outcomes [179].

5.3 Future research

I intend to implement the findings garnered from this thesis and pursue further research in vascular access to ensure that patients receive the best quality of care available. With access to a vascular laboratory, preoperative arterial waveform analysis could be carried out, which can identify individuals in need for more detailed arterial duplex mapping or angiography, highlighting arterial stenoses which can be addressed prior to fistula formation. Determining the role of ultrasound surveillance of fistulae, its effectiveness in predicting fistula maturation and whether surveillance can extend secondary patency by early identification of a "failing fistula" are questions which still have not been definitively addressed in the literature [39,180]. Identifying patients at risk of non-maturation, coupled with early assessment and prompt recognition of a failing or "failing to mature" fistula would allow for rapid intervention, ensuring continued dialysis via autogenous fistula [49]. Whether these interventions should involve open surgery or endovascular techniques would depend on each centre's strengths and available facilities, and there needs to be clear guidance in this respect [181]. Whether pre-emptive intervention should be performed is also a matter of contention, with a recent Cochrane review finding that it did not enhance access longevity, while possibly resulting in an increase in access-related procedures and consequently procedure related adverse events [182] .

6 REFERENCES

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7 APPENDICES

7.1 Ethical approval (Chapter 2)

NRES Committee London - East
REC Offices
Room 10, 4th Floor West
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
Telephone: 020 3311 7227
Facsimile: 020 3311 7280

Mr Gavin Pettigrew
Honorary Consultant Surgeon
Department of Surgery, Box 202,
Level E9, Addenbrooke's Hospital
Hills Road,
Cambridge CB2 0QQ

04 November 2011

Dear Mr Pettigrew

Study title: **The role of digital brachial pressure index (DBI) in haemodialysis access-induced steal syndrome (HASS).**
REC reference: **11/LO/1352**
Protocol number: **N/A**
Amendment number: **AM01**
Amendment date: **29 September 2011**

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Consent Form	2	14 September 2011
Participant Information Sheet	2	14 September 2011
Protocol	2	14 September 2011
Notice of Substantial Amendment (non-CTIMPs)	AM01	29 September 2011

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/LO/1352:	Please quote this number on all correspondence

Yours sincerely

Revd Dr Joyce Smith
Chair

E-mail: atul.patel@imperial.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mr Stephen Kelleher*
Miss Wing Yang Liu

NRES Committee London - East

Attendance at PRS Sub-Committee of the REC meeting on 27 October 2011

Name	*Profession*	*Capacity*
Mrs Sylvia Clarke	Retired / Lay Member	Lay
Elaine Mason	Retired Pharmacist	Lay
Ms Lindsay Royan	Consultant Clinical Psychologist	Expert
Revd Dr Joyce Smith	Chair - Clergy/Consultant Dentist	Expert
Dr Elizabeth Webster	General Practitioner	Expert

Also in attendance:

Name	*Position (or reason for attending)*
Mr Atul Patel	Proportionate Review Service Coordinator

7.2 Ethical Approval (Steal Trial)

NHS
National Research Ethics Service
Cambridgeshire 2 Research Ethics Committee
Victoria House
Capital Park
Fulbourn
Cambridge
CB21 5XB

Telephone: 01223 597685
Facsimile: 01223 597645

15 February 2011

Mr Gavin Pettigrew
Department of Surgery, Box 202,
Level E9, Addenbrooke's Hospital
Hills Road, Cambridge
CB2 0QQ

Dear Mr Pettigrew

Study Title: **Randomised controlled trial comparing the incidence of Steal syndrome in the two types of anTEcubital fossa Arteriovenous fistuLa: brachial artery versus proximal radial/ulnar artery as arterial inflow.(STEAL Trial)**

REC reference number: **10/H0308/90**

Thank you for your letter of 04 February 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Investigator CV	Gavin Pettigrew	
Response to Request for Further Information	Wing Yan Liu	04 February 2011
Protocol	3	04 February 2011
Covering Letter	Wing Yan Liu	13 September 2010
Participant Information Sheet	2	
REC application	45483/148801/1/501	13 September 2010
Participant Consent Form	2	
Evidence of insurance or indemnity	University of Cambridge	27 August 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H0308/90	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

p.p. NStorey

Dr Rowan Burnstein
Chair

Email: Nicky.Storey@eoe.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: Research and Development Department
Box 277
Addenbrooke's Hospital
Cambridge
CB2 0QQ

7.3 Participant Information Sheet

Addenbrooke's Hospital NHS
Cambridge University Hospitals NHS Foundation Trust

Participant Information Sheet

Randomised Controlled Trial on

Antecubital Fossa

Arteriovenous Fistula

and Steal Syndrome

(STEAL Trial)

Version 4

11th December 2013

We would like to invite you to take part in our research study. Before you decide we would like you to understand the purpose of this study and what it would involve if you participate. One of our research team will go through the information sheet with you and answer any questions you have.

Part 1: Background of Study

1.1 What is arteriovenous fistula?

An artery is a blood vessel through which blood flows from the heart to the rest of the body. A vein is a blood vessel through which blood collected from different parts of the body returns to the heart.

An arteriovenous fistula (AVF) is a connection between an artery and a vein. An AVF for haemodialysis is surgically created by joining the vein to the artery. This allows the vein to grow larger and stronger and provides easy access to the blood stream during dialysis.

1.2 Are there different types of AVF?

Yes. AVFs can be classified by the sites where they are created. They are mostly created on the arm but in rare cases they can be formed on the leg or ankle. In this study, we will look at elbow fistulae.

1.3 Why do you need an elbow fistula?

The strategies in creating AVFs for dialysis is to start in an area furthest from the trunk and if that fails, to form it closer to the trunk. For example, in the arm, the preferable site for AVF is the wrist, followed by the middle part of the forearm and then the elbow.

In case of no suitable vessels available for AVF creation in the wrist or forearm, either because the vessels are too small or contain clots, we will create an elbow fistula.

1.4 What are the risks of having an AVF? What is Steal Syndrome?

As in any other surgical procedure, creation of AVF can be complicated by bleeding and infection. Bleeding can occur immediately after the operation or can be prolonged after needling during dialysis. If infection occurs, most of the time it can be treated with antibiotics but in some cases it can lead to loss of the AVF.

Other risks include clot forming within the AVF, narrowing of the vessels close to the AVF and failure of the vein to expand. All of these can cause failure of the AVF.

Steal syndrome is another complication that can occur following AVF creation. It is caused by the decreased blood supply to the hand because blood is 'stolen' from the artery to the vein. It can cause a cold and pale hand, numbness, pain and, if left untreated, it can cause death of tissue in the hand ranging from ulcers to loss of fingers in severe cases. It is therefore important to recognise symptoms of steal early. There are different treatments for steal syndrome; in severe cases the fistula is tied off.

1.5 Who is at risk of getting steal syndrome?

All patients with AVFs are at risk of developing steal syndrome. Studies have shown that people with diabetes are at higher risk of getting steal. It has also been found that Steal occurs more frequently in elbow fistulae than in mid-forearm or wrist fistulae.

1.6 Why does an elbow fistula have a higher risk of steal syndrome?

An elbow fistula is usually created using the main artery called the brachial artery. This artery divides into two smaller arteries named the radial artery and the ulnar artery. It is believed that an AVF using the brachial artery can potentially disturb the blood flow in both the radial and ulnar arteries, whereas an AVF below the elbow only involves one of the two arteries, therefore the blood supply to the hand is less likely to be disturbed in a wrist or mid-forearm fistula.

On the basis of this theory, some surgeons have suggested that using either the radial or ulnar artery instead of the brachial artery can reduce the risk of steal syndrome in elbow fistulae. In this study, we aim to find the clinical evidence to support this theory.

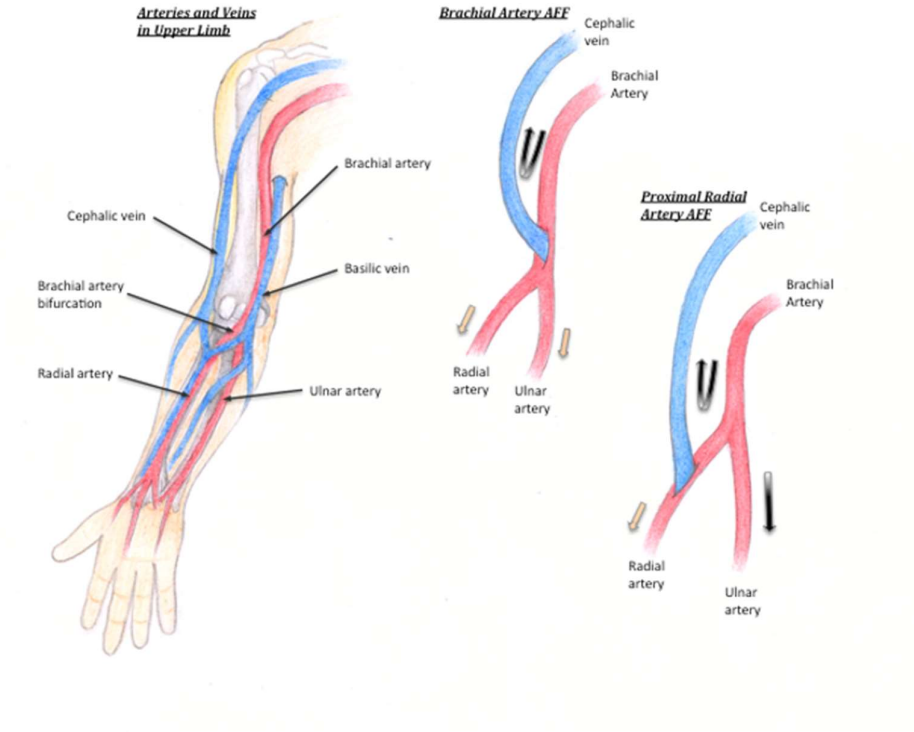


Figure 1. Distribution of blood vessels in the arm. The brachial artery divides into radial and ulnar artery at elbow level. An AVF using brachial artery affects blood flow to both branches, whilst the other type of AVF only affects one branch.

Part 2: Purpose of Study and Study Procedure

2.1 What is the purpose of the study?

The purpose of the study is to compare the two surgical methods in creation of an elbow fistula using either the brachial artery or one of its two branches - the radial or ulnar artery. The aim of our study is to find out if the latter method has a lower risk of causing Steal Syndrome. The result of this study will help future surgeons decide which method they can use to reduce the risk of steal syndrome.

2.2 Why have I been invited?

You are invited to take part in this study because you are going to have an elbow fistula. An elbow fistula is considered to be the best option for you because there is no suitable vessel in your wrist or forearm for creation of an AVF.

2.3 Do I have to take part?

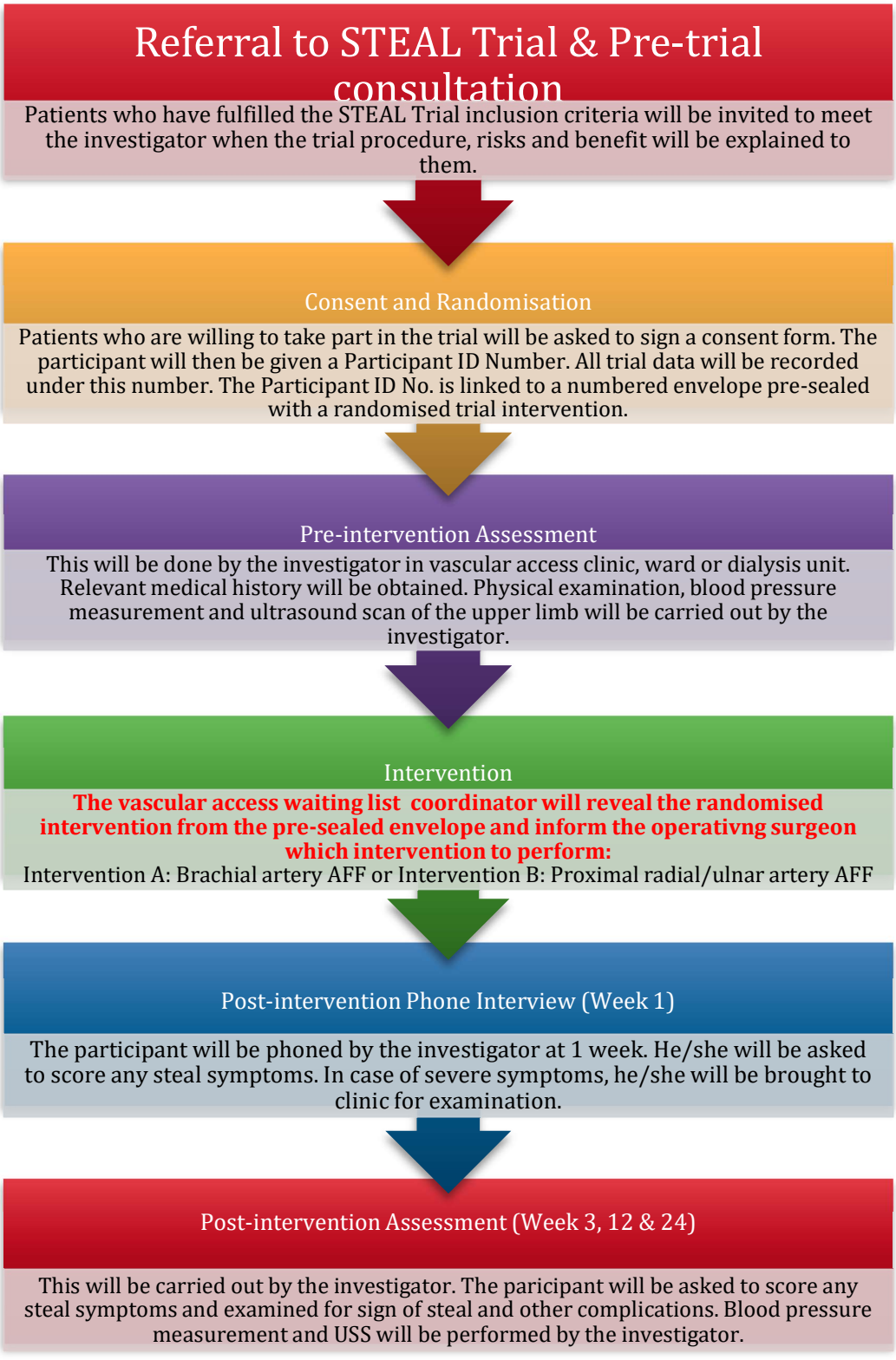
It is up to you to decide whether to take part in the study. We will explain to you what the study will involve, its risks and benefits and will go through this information sheet with you before you make a decision. If you decide to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

2.4 What will happen to me if I take part?

Your participation in this study will be approximately 7 months from the time you are approached by the investigator.

This is blinded randomised trial. A randomised trial means that you will be allocated to one of the study interventions by chance (randomly). We don't know which of the two study interventions is better for patients. We therefore put patients into two groups randomly and each group undergoes one intervention. The results are compared to see which one is better. **You will be 'blinded' i.e. you will not be told which intervention group you are in.**

Once you are identified as a potential participant for the trial, you will be approached by the investigator either when you are in the clinic, or in the ward if you have been admitted, or by phone. The investigator will explain to you briefly about the trial. If you are interested in taking part, you will then undergo the following ***Trial Procedures***.


Referral to STEAL Trial & Pre-trial consultation
Patients who have fulfilled the STEAL Trial inclusion criteria will be invited to meet the investigator when the trial procedure, risks and benefit will be explained to them.
Consent and Randomisation
Patients who are willing to take part in the trial will be asked to sign a consent form. The participant will then be given a Participant ID Number. All trial data will be recorded under this number. The Participant ID No. is linked to a numbered envelope pre-sealed with a randomised trial intervention.
Pre-intervention Assessment
This will be done by the investigator in vascular access clinic, ward or dialysis unit. Relevant medical history will be obtained. Physical examination, blood pressure measurement and ultrasound scan of the upper limb will be carried out by the investigator.
Intervention
The vascular access waiting list coordinator will reveal the randomised intervention from the pre-sealed envelope and inform the operativng surgeon which intervention to perform:
Intervention A: Brachial artery AFF or Intervention B: Proximal radial/ulnar artery AFF
Post-intervention Phone Interview (Week 1)
The participant will be phoned by the investigator at 1 week. He/she will be asked to score any steal symptoms. In case of severe symptoms, he/she will be brought to clinic for examination.
Post-intervention Assessment (Week 3, 12 & 24)
This will be carried out by the investigator. The paricipant will be asked to score any steal symptoms and examined for sign of steal and other complications. Blood pressure measurement and USS will be performed by the investigator.

2.5 Expenses and payments

Travel expenses will be available when you make a trip to Addenbrooke's Hospital for the pre-intervention assessment and follow-up assessments. If you require hospital transport, we will arrange that for you. If you use your own transport, please keep your receipts or let us know the distance you have travelled, so that we can help you to claim your travel expenses.

2.6 What will I have to do?

You will need to attend all the scheduled pre-trial interviews and assessment, the trial intervention and follow-up assessments as described in Section 2.4.

2.7 What are the possible disadvantages and risks of taking part?

The risks of taking part in this study are no different from the risks associated with any fistula creation. Please refer to Section 1.4 to 1.6 for the risks of elbow fistula. If you are randomised to undergo Intervention B (proximal radio/ulnar artery AVF), the operation will take approximately 10 to 15 minutes longer than Intervention A (brachial artery AVF). The risk of getting minor complications such as bleeding, infection and clots has no difference between the two study interventions.

Based on the clinical assessments by your nephrologist and the transplant surgeon, it has already been decided that an elbow fistula is the most appropriate means for you to have haemodialysis. The two surgical methods involved in this trial are both regularly used in creation of elbow fistulae. You would undergo one of these two procedures even if you were not involved in this study. The only difference is that the decision of which procedure you will undergo will be made by the trial randomisation process if you take part. This would otherwise be decided by the operating surgeon according to the individual surgeon's preference and assessment.

2.8 Radiation and the Ionising Radiation (Medical Exposure) Regulations (IRMER)

You will have a series of ultrasound scans to assess the blood vessels in your arms throughout this study. This does not involve any radiation or ionising radiation.

2.9 What are the possible benefits of taking part?

We will follow you up more closely after your AVF creation. Patients who have had AVF creation would generally be seen at Vascular Access Clinic once after the procedure or be followed up at their routine Nephrology Clinic. As a trial participant, you will be followed up by the investigator at 1 week (by phone), 3 weeks, 3 months and 6 months after the procedure. The investigator will pay special attention to any complications that could arise so they can be treated as early as possible.

2.10 What happens when the research study stops?

At the end of your participation, we will notify your nephrologist in writing so that you will continue your follow up at your local Nephrology Clinic or Dialysis Unit.

You will receive a report on the study results and will be told which study group you have been in at the end of study. We estimate that it will take 3 years to complete this study.

2.11 What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 3.

2.12 Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 3.

Part 3 Study Information, Medico-Legal and Ethical Issues

3.1 What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, the investigator will tell you and discuss whether you should continue in the study. If you decide to not to carry on, the investigator will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an agreement outlining the discussion.

3.2 What happens if I don't want to carry on with the study?

You may withdraw at any stage of the study, either before or after the study intervention. If you withdraw after you have had the study intervention, information collected up to the point of your withdrawal may still be used for study analysis.

3.3 What if there is a problem?

Complaints

If you have a concern about any aspect of this study, you should ask to speak to the investigators who will do their best to answer your questions *(You will find the contact details of the investigators at the end of this information sheet)*. If you remain unhappy and wish to complain formally, you can do this via the *NHS Complaints Procedure.*

Harm

In the event that something goes wrong and you are harmed during the research, and this is due to someone's negligence, then you may have grounds for a legal action for compensation against *Cambridge University Hospitals NHS Foundation Trust*, but you may have to pay your legal costs. The normal *National Health Service complaints mechanisms* will still be available to you.

3.4 Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential.

Once you take part in this study, you will be given a Participant ID Number. All the data we collect from you will be recorded and stored under this number. Only authorised persons (i.e. investigators, trial staffs and Research & Development personnel who are responsible for monitoring of quality of the study) will have the access to view identifiable data.

3.5 Involvement of the General Practitioner (GP)

It is not necessary to notify your GP about your participation in the study. A discharge letter will be sent to your GP as a routine procedure after your operation but this is not part of the study procedure.

3.6 What will happen to the results of the research study?

We intend to publish the results of this study in scientific journals. We will send you a report of the study once the results are available. You will not be identified in any report or publication.

3.7 Who is organising and funding the research study?

The study is organised and conducted by the Department of Surgery, Cambridge University Hospitals NHS Foundation Trust.

The study is funded by NIHR Cambridge Biomedical Research Centre, Transplant Theme.

The investigators will not be paid for conducting the study. There is no conflict of interests.

3.8 Who has reviewed the study?

All research in the NHS is looked at by independent groups of people, called the Research Ethics Committees, to protect your interests. This study has been reviewed and given favourable opinion by Cambridgeshire 2 Research Ethics Committee.

3.9 Further information and contact details

For general information about research, please visit the Cambridge University Hospitals NHS Foundation Trust Research & Development website:

http://www.cuh.org.uk/research/public/public_index.html

OR contact:

Patient Advice & Liaison Service (PALS)

Cambridge University Hospitals NHS Foundation Trust

Tel: 01223 216756

Email: pals@addenbrookes.nhs.uk

For specific information about this research study and advice as to whether you should participate, please contact one of the investigators:

1. Mr Gavin Pettigrew (Chief Investigator)

Honorary Consultant Surgeon & Lecturer

Department of Surgery

Box 202, Level E9

Cambridge University Hospitals NHS Foundation Trust

Hills Road

Cambridge

CB2 0QQ

Email: gjp25@cam.ac.uk

Contact number: 01223 762523

2. Mr Aaron Goh (Investigator)

Clinical Research Fellow

Department of Surgery

Box 202, Level E9

Cambridge University Hospitals NHS Foundation Trust

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CB2 0QQ

Email: aaron.goh@addenbrookes.nhs.uk

Contact number: 01223 336975

If you are unhappy with the study, please contact one of the investigators or you could make a formal complaint via *NHS Complaints Procedure.* You could find this information in the following website:

http://www.nhs.uk/choiceintheNHS/Rightsandpledges/complaints/Pages/NHScomplaints.aspx

Addenbrooke's Hospital NHS
Cambridge University Hospitals NHS Foundation Trust

CONSENT FORM

Study Title: Randomised controlled trial on antecubital fossa AVF (STEAL Trial)

STEAL Trial Participant Identification Number: _____

Name of Investigator:

	Please initial box
1. I confirm that I have read and understand the information sheet dated _____ (Version _____) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4. I agree to my nephrologist being informed of my participation in the study.	☐
5. I agree to take part in the above study.	☐

Participant Signature: _____

Participant Name: _____ Date: _____

Signature of person taking consent: _____

Name of person taking consent: _____ Date: _____

7.4 Pre-intervention assessment form (steal trial)

Participant ID Number: _____ Date of Informed Consent: _____/_____/_____

Date of Pre-Intervention Assessment: _____/_____/_____ Dialysis Centre: _____

Demographic

Age: _____years Gender: M / F Ethnicity: _____ Dominant Hand: R / L

Smoking Hx: Smoker_____pack years / Ex-smoker, stopped for_____years / Non-smoker

Past Medical History

Renal Disease

Cause of ESRF: _____ Latest GFR: _____ on _____/_____/_____

Date commenced on long-term dialysis: _____/_____/_____ 1st vascular access used: Line / AVF

Dialysis Status: Pre-Dialysis / Haemodialysis / CAPD / CCPD Current Access: _____ L / R

AVF History:

1. ____/____/____ Type: _____ L / R Matured? Y / N Failure: ___/___/___ _____
2. ____/____/____ Type: _____ L / R Matured? Y / N Failure: ___/___/___ _____
3. ____/____/____ Type: _____ L / R Matured? Y / N Failure: ___/___/___ _____
4. ____/____/____ Type: _____ L / R Matured? Y / N Failure: ___/___/___ _____
5. ____/____/____ Type: _____ L / R Matured? Y / N Failure: ___/___/___ _____
6. ____/____/____ Type: _____ L / R Matured? Y / N Failure: ___/___/___ _____
7. ____/____/____ Type: _____ L / R Matured? Y / N Failure: ___/___/___ _____

Diabetes

Type 1 / Type 2 Age of Onset: _____ years DM Treatment: None / Diet / Oral / Insulin

Diabetic Complication(s): _____

Cardiovascular Disease

MI / Angina / LVF / HTN / AF Details: _____

Central venous stenosis: Y / N Details: _____

Peripheral Vascular Disease

Venogram ☐ Date: ____/____/____ Results: _____

MRA ☐ Date: ____/____/____ Results: _____

Angiogram ☐ Date: ____/____/____ Results: _____

Angioplasty ☐ Details: _____

Bypass ☐ Details: _____

Amputation ☐ Details: _____

Medications

Anticoagulant	☐	Details: _____
Antihypertensive	☐	Details: _____
Lipid-lowering agent	☐	Details: _____
Oral hypoglycaemic agent	☐	Details: _____
Insulin	☐	Details: _____
Steroids & Immunosuppressant	☐	Details: _____

Physical Examination

Height: _____cm Weight: _____kg BMI: _____

Vascular Assessment

Artery (pulses)	Right	Left
BA (N/W/A)		
RA at wrist (N/W/A)		
UA at wrist (N/W/A)		

N=normal; W=weak; A=absent

Vein		Right	Left
CV	Palpable to elbow		
	Tap test to elbow		
BV	Palpable to elbow		
	Tap test to elbow		

Ultrasonic Vascular Assessment

	Volume flow		

Artery		Right	Left
BA	Size (mm)		
	Calcification (Y/N)		
	High bifurcation		
	Volume flow		
RA elbow	Size (mm)		
	Calcification (Y/N)		
	Volume flow		
UA elbow	Size (mm)		
	Calcification (Y/N)		
	Volume flow		
RA wrist	Size (mm)		
	Calcification (Y/N)		
	Volume flow		
UA wrist	Size (mm)		
	Calcification (Y/N)		

Vein		Right	Left
CV	Size at wrist (mm)		
	Size at forearm (mm)		
	Size at elbow (mm)		
	Thrombus present		
	Site of thrombus		
BV	Size at wrist (mm)		
	Size at forearm (mm)		
	Size at elbow (mm)		
	Thrombus present		
	Site of thrombus		
MCV	MCV present (Y/N)		
	Size (mm)		

Examination of Hands

		Right	Left
Temperature (1= very cold, 5= very warm)			
Sensation (Normal/impaired/absent)	**Light touch** **Sharp touch** **2-point discrimination**		
Muscle wasting (1= none, 5= very severe)			
Power (1-5)	**Thumb adduction** **Grip strength**		
Skin colour (Normal/Pallor/Cyanosed)			
Tissue loss (None/Ulcer/Gangrene/Loss of digit)			
Capillary refill time (in seconds)			

Hoek Score

	Right			Left		
	Severity	**Frequency**	**Subtotal**	**Severity**	**Frequency**	**Subtotal**
Cold Hand						
Pain						
Altered sensation						
Reduced Strength						
Cramps						
Total						

Digital Brachial Pressure Index

	Right	Left
Brachial BP	/	/
DP at rest	Index/Middle	Index/Middle
DP after exercise	Index/Middle	Index/Middle
DBPI at rest		
DBPI after exercise		

CHECKLIST FOR ELIGIBILITY

Age 16 years and above	☐	Not suitable for wrist or forearm AVF	☐
Diagnosed with ESRF	☐	BA & PRA/PUA could be used for AFF	☐
On or due to commence on haemodialysis	☐	Vein availble in both BA & PRA/PUA territories	☐

PROPOSED VENOUS OUTFLOW: Cephalic / Basilic / Other:_____ **SIDE:** R / L

PROPOSED DATE OF INTERVENTION: _____/_____/_____ **ANAESTHESIA:** LA / GA

7.5 Trial-specific operation record (steal trial)

Participant ID Number: _____ Date: _____/_____/_____ Day case / Inpatient

Operating Surgeon: _____Assistant: _____

Anticoagulant(s): _____Stopped pre-op: Y / N INR (if on Warfarin): _____

Type of Anaesthesia: General / Local / Regional block, please specify:_____

PRE-OP ULTRASOUND ASSESSMENT (please only record finding for AFF arm) **Side: R / L**

USS performed by operating surgeon ☐

Both BA and PRA/PUA patent ☐ If not, please give details: _____

RANDOMISED INTERVENTION PERFORMED: YES / NO

If NO, please give reason:_____

_____

INTERVENTION: CREATION OF AFF

Vein used for AFF

Vein: CV / BV / Others:_____

Diameter: _____mm, distended to _____mm

Quality of vein [please tick as appropriate]:

Normal ☐

Fibrotic ☐

Thin & fragile ☐

Arterialised vein ☐

Artery used for AFF

Artery: BA / PRA / PUA

Diameter: _____mm

If PRA/PUA-AVF created, which artery has smaller calibre?
PRA / PUA

Quality of artery

Normal Artery ☐

Atherosclerosis ☐

Endarterectomy performed ☐

Arterial flow: Excellent / Good / Adequate / Poor

Anastomosis

Length of arteriotomy:_____mm Type of suture:_____Continuous / Interrupted

OUTCOMES

Thrill presents after anastomosis ☐

Thrill presents after skin closure ☐

No thrill but bruit presents on closure ☐

Anastomosis taken down & Redo ☐

Haemorrhage after closure ☐

Return to theatre within 24 hours ☐

Predicted Chance of Success:_____%

7.6 Post-intervention assessment form (steal trial)

Participant ID Number: _____ Date of Intervention: _____/_____/_____

Types of Venous Outflow: Cephalic / Basilic / Other: _____ Side: R / L

Date of Assessment: _____/_____/_____ 1-week (phone) / 3-week / 3-month / 6-month

IF EXPERIENCED ANY STEAL SYMPTOMS, please state DATE OF ONSET:_____/_____/_____

HOEK SCORE

	Right			Left		
	Severity	**Frequency**	**Subtotal**	**Severity**	**Frequency**	**Subtotal**
Cold Hand						
Pain						
Altered sensation						
Reduced Strength						
Cramps						
Total						

EXAMINATION OF HANDS ***(except week 1 assessment)***

		Right	Left
Temperature (1= very cold, 5= very warm)			
Sensation (Normal/impaired/absent)	**Light touch** **Sharp touch** **2-point discrimination**		
Muscle wasting (1= none, 5= very severe)			
Power (1-5)	**Thumb adduction** **Grip strength**		
Skin colour (Normal/Pallor/Cyanosed)			
Tissue loss (None/Ulcer/Gangrene/Loss of digit)			
Capillary refill time (in seconds)			

DIGITAL BRACHIAL PRESSURE INDEX

	AFF side	Contralateral side	AFF side (compressed)
Brachial BP	N/A	/	N/A
DP at rest	Index/Middle	Index/Middle	Index/Middle
DP after exercise	Index/Middle	Index/Middle	Index/Middle
DBPI at rest			
DBPI after exercise		N/A	N/A

ASSESSMENT OF AFF

Clinical Examination

Thrill palpable / No thrill but bruits audible / No thrill or bruits

Ultrasound

AFF patent: Y / N Size of vein: Perianastomotic _____mm / 5cm proximal_____mm

Fistula volume flow: _____ml/min (Mean D:_____mm; Mean TAM:_____)

Thrombosis: Y / N Site: _____ Stenosis: Y / N Site: _____

Local Complications **(Please record event which occurred after last post-interventional assessment)**

Post-op bleeding	☐	Resolves without Tx / Medical Anticoagulation / Intervention
Post-needling bleeding	☐	Resolves without Tx / Medical Anticoagulation / Intervention
Anastomosis bleeding	☐	Resolves without Tx / Aspiration or drainage / Loss of access
Other fluid collection	☐	Resolves without Tx / Aspiration or drainage / Loss of access
Infection	☐	Resolves with Abx / Loss of access / Loss of limb
		Site: Wound / Perianastomotic / Mid-access / Run-off vein
		Culture date:_____/_____/_____Results:_____
Pseudoaneurysm	☐	Resolves without Tx / Functional after Tx / Loss of access
		Site: Anastomosis / Needled site
Stenosis	☐	Resolves without Tx / Functional after Tx / Loss of access
		Site: Perianastomotic / Mid-access / Run-off vein
Thrombosis	☐	Clot removed / Revision / Loss of access
		Cause: Not found / Technical / Intimal hyperplasia / Coagulation

UTILISATION OF AFF

Date of first cannulation: _____/_____/_____

Date of commencement of regular dialysis: _____/_____/_____ Maturation: _____weeks

Most recent dialysis flow rate via AFF: _____ml/min Haemodialysis Clearance: _____%

Problems with dialysis: None / Poor inflow / Poor outflow / Prolonged bleeding / Difficult cannulation

Others, please specify: _____

PLAN FOR INVESTIGATION: **None** ☐ **Doppler/Duplex** ☐ **MRA** ☐ **Angiogram** ☐

PLAN FOR INTERVENTION: **Angioplasty** ☐ **Surgical revision** ☐ **Ligation of AFF** ☐